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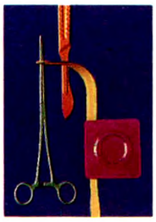
+ more cost-effective than cefoxitin[1,2]

− less frequent dosing than cefoxitin[3,4]

× several times the half-life of cefoxitin[5,6]

÷ single-dose prophylaxis/ twice-daily treatment



Count on
CEFOTAN® IM/IV
(cefotetan disodium)
In intra-abdominal and gynecologic infection due to indicated organisms

References: **1.** Nightingale CH, Smith KS, Quintiliani R, et al: The conversion of cefoxitin usage to cefotetan: An interdisciplinary approach. *Am J Surg* 1988;155(5A):101-102. **2.** Sochalski A, Sullman S, Andriole VT: Cost-effectiveness study of cefotetan versus cefoxitin and cefotetan versus combination antibiotic regimens. *Am J Surg* 1988;155(5A):96-101. **3.** CEFOTAN® (cefotetan disodium) full prescribing information issued March 1986. **4.** *Physicians' Desk Reference*, ed 43. Oradell, NJ, Medical Economics Co, 1989. Mefoxin® (cefoxitin sodium, MSD), pp 1355-1357. **5.** Carver M, Quintiliani R, Nightingale CH: Comparative pharmacokinetic study of cefotetan and cefoxitin in healthy volunteers. *Infect Surg*, April 1986 (suppl), pp 11-14. **6.** Quintiliani R, Nightingale CH, Stevens RC, et al: Comparative pharmacokinetics of cefotetan and cefoxitin in patients undergoing hysterectomies and colorectal operations. *Am J Surg* 1988;155(5A):67-70.

Please see adjacent page for brief summary of prescribing information.

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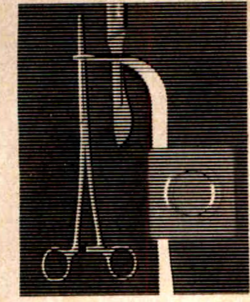

Count on

CEFOTAN® IM/IV

(cefotetan disodium)

In intra-abdominal and gynecologic infection due to indicated organisms

For Intravenous or Intramuscular Use
BRIEF SUMMARY

INDICATIONS AND USAGE

TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:

Urinary tract infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris, Providencia rettgeri*, and *Morganella morganii*).

Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli.*

Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli.*

Gynecologic infections caused by *Staphylococcus aureus** (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus* species (excluding enterococci), *E coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*), *Fusobacterium* species,* and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species*).

Intra-abdominal infections caused by *E coli, Klebsiella* species (including *K pneumoniae**), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*).

Bone and joint infections caused by *Staphylococcus aureus.**

*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, it is possible to use CEFOTAN concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic in vitro against many Enterobacteriaceae and also some other gram-negative bacteria. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition.

NOTE: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.

CONTRAINDICATIONS

CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile.* Other causes should also be considered.

PRECAUTIONS

GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, the elderly and patients with cancer. Prothrombin times should be monitored in patients at risk and exogenous vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.

INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc.) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.

DRUG INTERACTIONS: Although to date nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.

DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffe reaction and produce false increases in the levels of creatinine reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.

USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

In clinical studies, the following adverse effects were considered related to CEFOTAN therapy.

Gastrointestinal symptoms occurred in 1.5% of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).

Hematologic laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).

Hepatic enzyme elevations occurred in 1.2% of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).

Hypersensitivity reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700).

Local effects were reported in less than 1.0% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500). During postmarketing experience with CEFOTAN, anaphylactic reactions and transient thrombocytopenia have been reported.

DOSAGE AND ADMINISTRATION

TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.

IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dosage*	Every 12 hours
10-30	Usual Recommended Dosage*	Every 24 hours
<10	Usual Recommended Dosage*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.

When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males:}\quad \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females:}\quad 0.9 \times \text{value for males}$$

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.

HOW SUPPLIED

CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. CEFOTAN is also available in a pharmacy bulk package of 10 g in 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21); 10 g in 100 mL vial (NDC 0038-0375-10).

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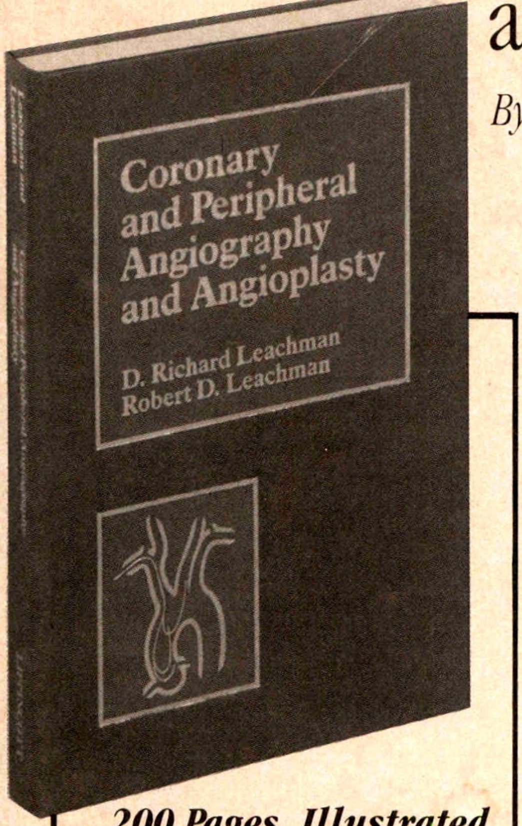

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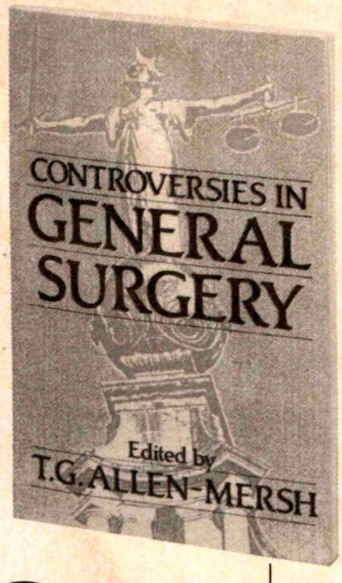

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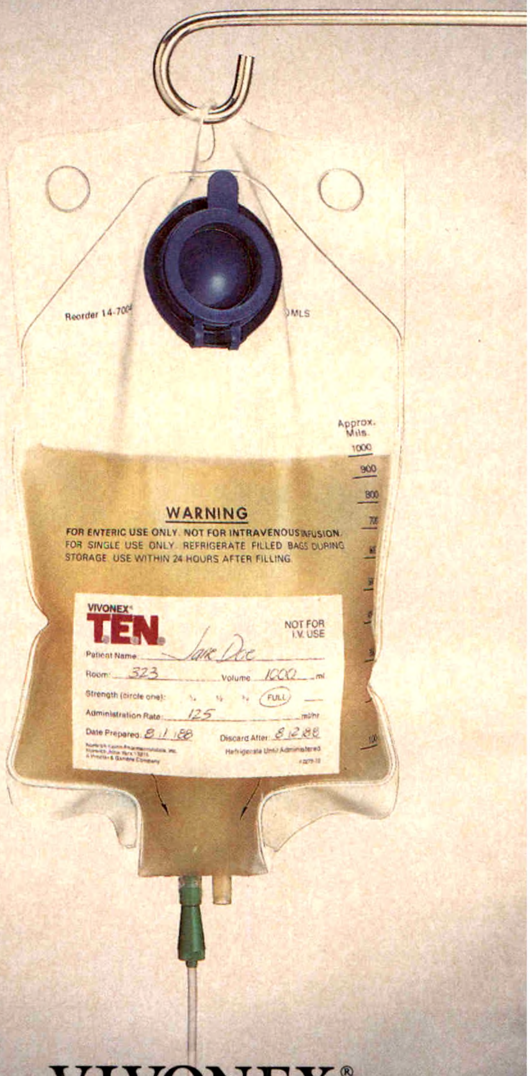
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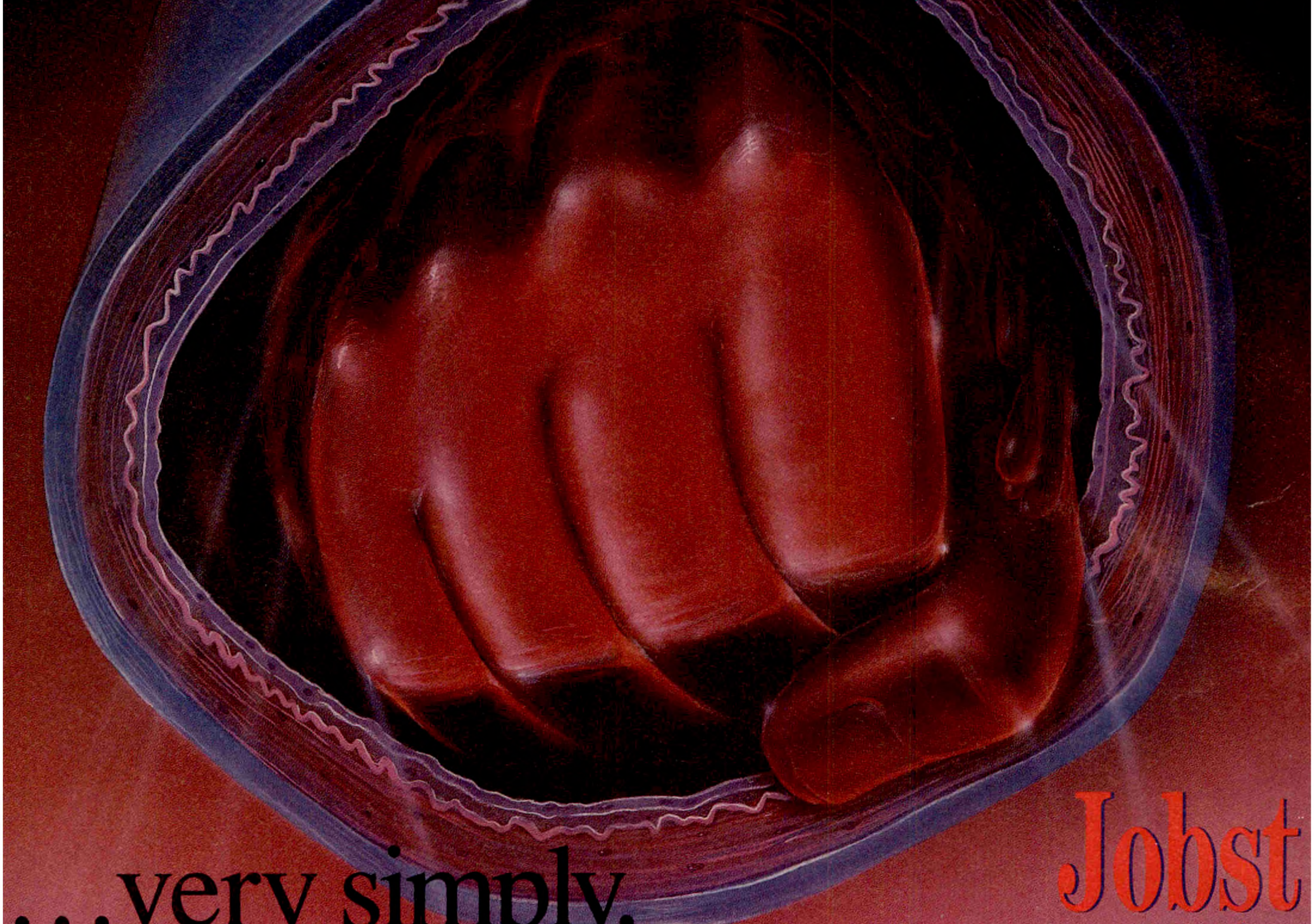

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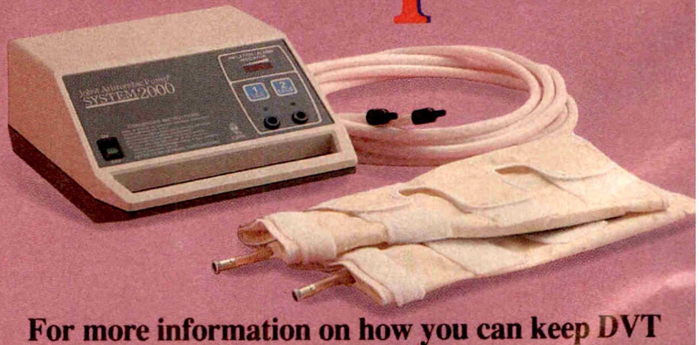

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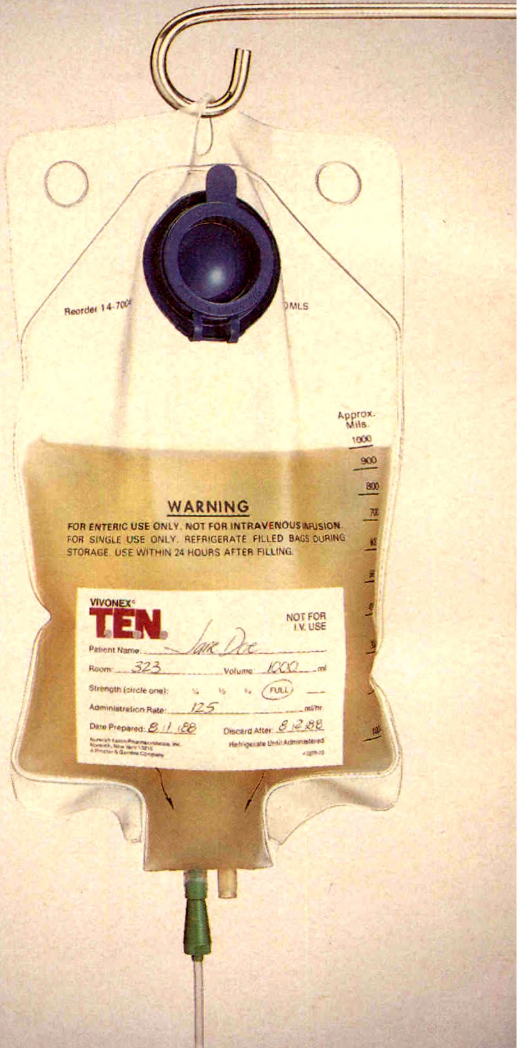
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Samuel A. Wells, Jr., M.D.
St. Louis, Missouri

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A detailed study of 1232 patients with carcinoma of the breast managed by quadrantectomy, axillary dissection, and radiation therapy with favorable results. Emphasis is placed on the importance of early diagnosis and treatment.

U. Veronesi, B. Salvadori, L. Luini, A. Banfi, R. Zucali, M. Del Vecchio, R. Saccozzi, E. Beretta, P. Boracchi, G. Farante, V. Galimberti, G. Mezzanotte, V. Sacchini, S. Tana, and E. Marubini
Milan, Italy

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The morbidity and mortality after exploration of the common duct was shown to be low, with a morbidity rate of 7.4% and no deaths.

T. N. Pappas, M.D.*, T. B. Slimane,* M.D.*, and D. C. Brooks,* M.D.
Durham, North Carolina; Avril, Tunis; and Boston, Massachusetts

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Yoichi Murayama, M.D.
Tokyo, Japan

Supplemental Vitamin A Prevents the Tumor-induced Defect in Wound Healing **269**

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Jeffrey Weinzweig, M.D.*, Stanley M. Levenson,* M.D.*, Giuseppe Rettura,* PH.D.*, Norman Weinzweig,* M.D.*, Josef Mendecki,* PH.D.*, Tsueng H. Chang,* PH.D.*, and Eli Seifter,* PH.D.
Bronx, New York and Detroit, Michigan

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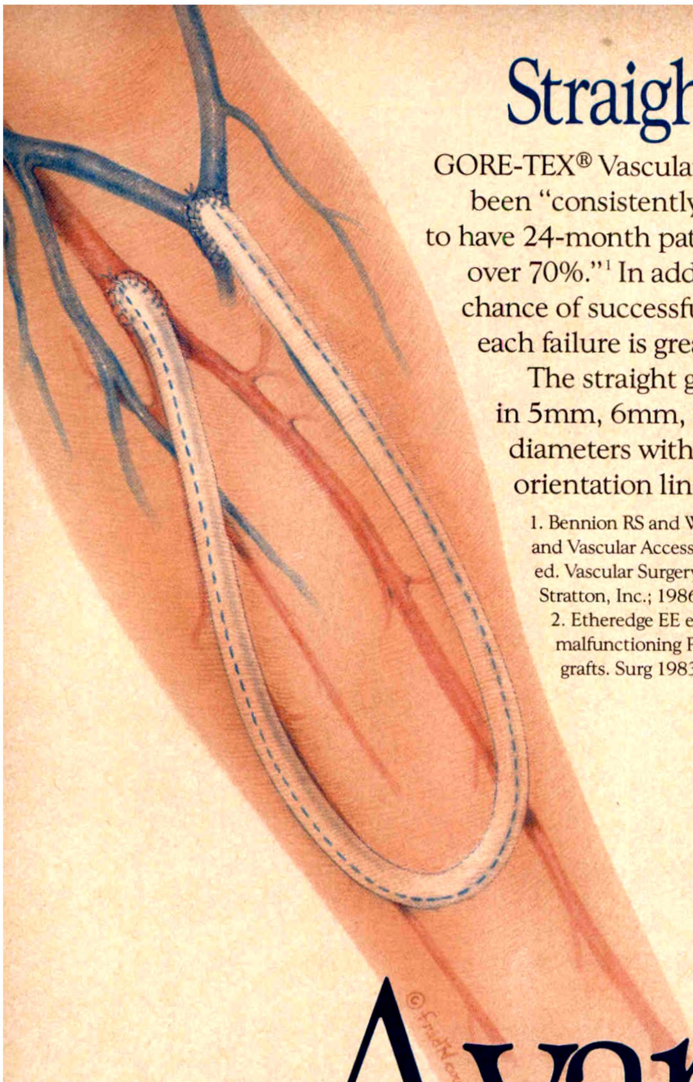

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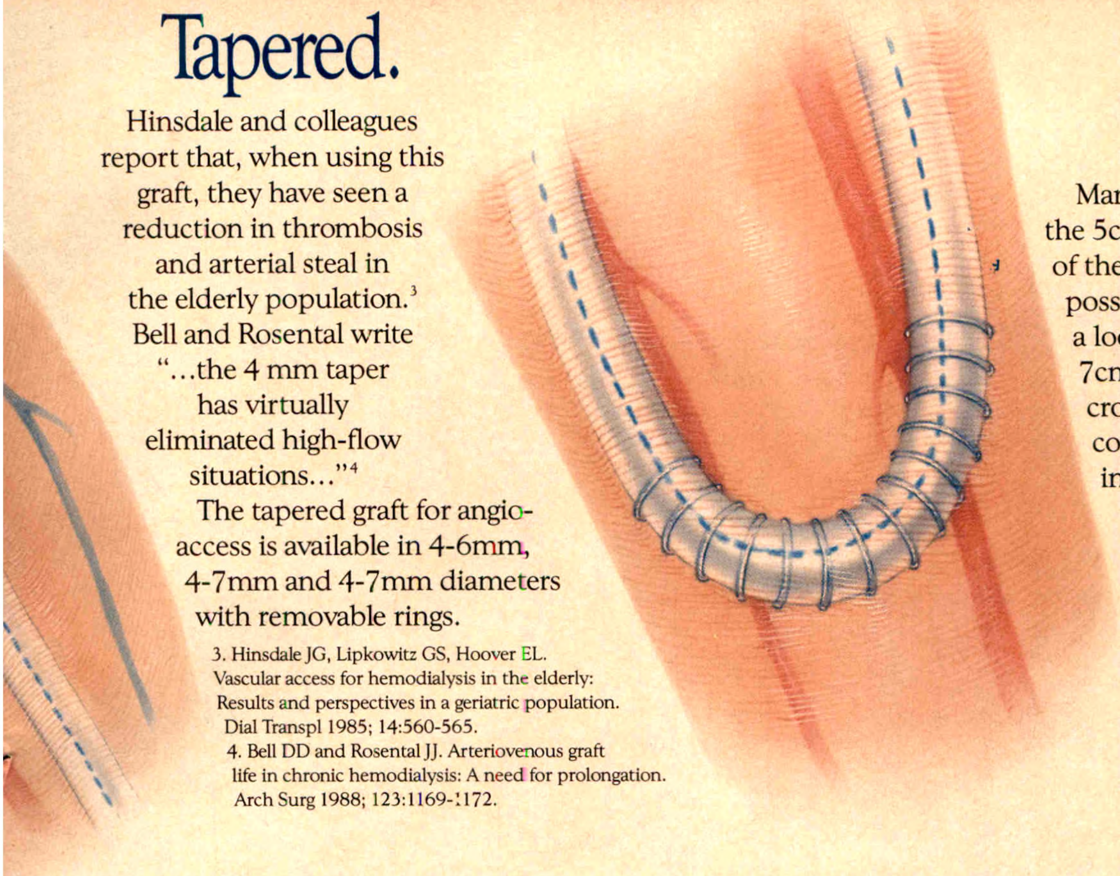

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The Liver Cancer Study Group of Japan
Kyoto, Japan

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George A. Ksander, A.M., *Yasushi Ogawa,* PH.D., *George H. Chu,* M.S., *Hugh McMullin,* B.S.,
Joel S. Rosenblatt, PH.D., *and John M. McPherson,* PH.D.
Palo Alto, California

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A. Hon Kwon, M.D., *Shoji Uetsuji,* M.D., *Manabu Yamamura,* M.D., *Koshiro Hioki,* M.D.,
and Masakatsu Yamamoto, M.D.
Osaka, Japan

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What's New In General Surgery

Hepatic Resection

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The current performance and applicability of elective hepatic resection represents an impressive evolution. From removal of tumor-bearing, ill-defined portions of the liver, which is always threatened by the inability to control bleeding, surgery of the liver has progressed to hemostatically controlled dissection of anatomically defined portions of the organ. Accompanying the series of technical refinements that have markedly reduced the mortality and morbidity rates associated with the procedure, there has been an expansion of the indications for hepatic resection.

HEPATIC RESECTION CAN be traced through three distinct periods based on perception of the anatomy of the liver. In the first period, portions of the liver were removed without regard for intrahepatic planes, and it was taught that the liver was divided solely along the line of the falciform ligament.

The second period stemmed from a revised appreciation of the anatomy of the liver. In 1898 Cantlie[1] used casts to demonstrate that the main lobar fissure extended from approximately the bed of the gallbladder anteroinferiorly to the right side of the inferior vena cava posterosuperiorly. This work was extended by Hjörtsjo[2] and by Healey and Schroy,[3] who demonstrated that the right lobe was divided into an anterior and posterior segment and that the left lobe was divided into a medial and lateral segment by the line of the falciform ligament. The understanding of this anatomy led to development of surgical planes of the liver and to anatomic resection along these intersegmental planes.

More recently Couinaud[4] refined the anatomic concept and demonstrated that the two lobes of the liver actually were hemilivers that consisted of eight segments, each of which, theoretically, could be resected.

The first elective removal of a liver lesion was reported in 1886 by Luis,[5] who removed an adenoma; in this case the patient died. The first successful elective hepatic resection is credited to Langenbuch[6] who, in 1888, excised a portion of the left lobe of the liver. That patient required re-exploration for internal hemorrhage a few hours after the operation and the patient survived. Tiffany,[7] in 1890, was the first American surgeon to report a case of hepatic resection for tumor, and the following year Lücke[8] reported the first successful removal of a malignancy from the left lobe of the liver. In 1892 Keen[9] reported the excision of a cystic adenoma of the bile ducts within the liver using a technique of ligature through the base of the tumor, cautery, and stripping the liver from the tumor with a thumbnail. This article included the first collective review in which 20 cases were extracted from the liver. In 1899 the same author performed the first successful left lobectomy for cancer of the liver, a procedure we would today term left lateral segmentectomy.[10] In this

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operation five vessels were ligated individually with catgut and cautery was applied to the raw surface. Wendel[11] reported the first case of near-total right lobectomy for primary tumor in 1911.

The major problem confronting the surgeon during hepatic resection, both in the past and today, has been hemorrhage control. In 1896, during the early historical period, Kousnetzoff and Pensky[12] devised the use of blunt needles and the application of ligatures to isolated blood vessels when the parenchyma was transected. One year later Auvray[13] described a series of mattress sutures that resembled those suggested by Kousnetzoff and Pensky, and first he applied the technique to humans. Ten years later in the United States, Hough[14] described using a series of mattress sutures with a crossover to permit approximation of the Glisson's capsule to effect tamponade.

The next approach to managing bleeding from the hepatic parenchyma was that of temporary inflow occulsion, which is still called the Pringle maneuver. In 1908 J. Hogarth Pringle, a Scottish surgeon, published an article in the *Annals of Surgery* on the arrest of hepatic hemorrhage due to trauma.[15] He reported on eight patients with hepatic trauma, only four of whom had undergone operation. Two of these patients died on the operating room table, and the remaining two patients died shortly thereafter. It is interesting that, given this data, the technique was ever adopted. Unquestionably the adoption of the technique was based on Pringle's experiments on rabbits, which demonstrated that inflow occlusion could effectively reduce bleeding from the transected hepatic parenchyma.

In 1940 Cattell[16] reported the successful removal of a liver metastases from a primary lesion in the colon. In 1943 Wangensteen[17] reported coincidental partial hepatectomy for gastric carcinoma involving the liver by direct extension. In 1948 Raven[18] reported a left lateral segmentectomy for metastatic colon cancer in which the triangular and coronary ligaments were transected and the left hepatic artery, left portal vein, and the left bile duct were ligated within the hepatoduodenal ligament. The left hepatic vein was isolated extrahepatically, after which the parenchyma was transected.

The modern era of hepatic resection dates from the 1952 report of Lortat-Jacob and Robert[19] in which the blood vessels and bile duct to the right lobe were ligated within the hepatoduodenal ligament and the right hepatic vein was ligated extrahepatically before transection of the hepatic parenchyma. In 1953 Quattlebaum[20] reported three cases of major hepatic resection, one of which was the first recorded right lobectomy for primary hepatocellular carcinoma. Also in 1953 Mersheimer published a similar experience.[21]

A significant technical contribution, the so-called "finger fracture" has inappropriately been ascribed to Oriental surgeons. In 1903 Anschutz[22] demonstrated that when the liver parenchyma was disrupted digitally, only the intrahepatic portal pedicles and hepatic veins resisted. In his 1953 publication, Quattlebaum[20] described performing liver dissection with the handle of the scalpel and indicated that this permitted exposure of the intrahepatic vessels. In 1956 Fineberg et al.[23] reported dividing the parenchyma by means of his finger during a right lobectomy. The technique was popularized by Lin,[24] who applied it successfully to a large series of patients. The procedure was finally refined by Ton That Tung,[25] who combined inflow occlusion of the vessels and ducts within the hepatoduodenal ligament with "finger fracture" of the parenchyma. Couinaud[26] emphasized that "finger fracture (digitoclasia) should be a gentle technique and must be respectful of anatomy."

Indications for Elective Hepatic Resection

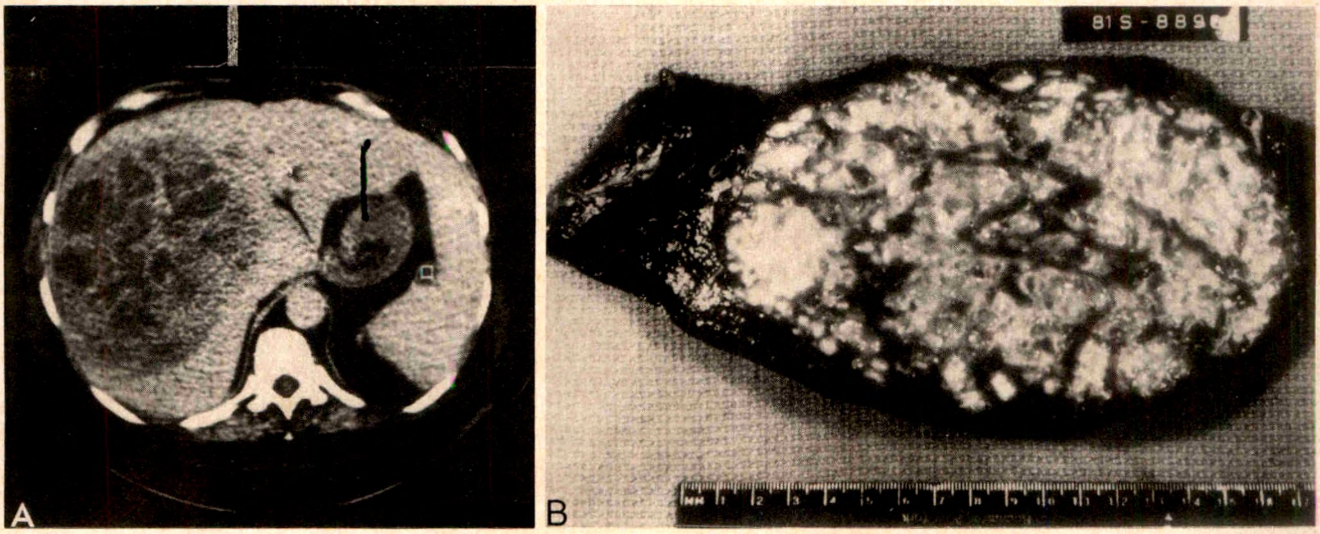
Resection of segments or a lobe of the liver may be indicated for a nonparasitic cyst, for localized granulomatous processes, and for diffuse multiple abscesses confined to a resectable area (Fig. 1). The most common benign primary lesion that may require resection for pain or a mass is a hemangioma[27] (Fig. 2). Hepatic-cell adenomas should usually be resected because of their potential to bleed either intraparenchymally (Fig. 3) or intraperitoneally, and the potential for malignant transformation.[28] Mesenchymal hamartoma is a rare, resectable tumor.

Primary hepatic malignancies that may be resected with the potential for cure are hepatocellular carcinoma, including follicular carcinoma, and hepatoblastoma. Some tumors that have metastasized to the liver are resected because of the potential for cure. Resection for metastases from the colon or rectum is associated with a 25% 5-year survival rate. Resection for hepatic metastases from Wilms' tumor has a survival rate of more than 50%. Occasional long-term survivals have been reported after hepatic resection for metastases from gastric, renal, and ovarian carcinomas and from occular melanomas. Significant palliation has been effected by a debulking resection of symptomatic carcinoids.

Advanced cirrhosis generally precludes a major hepatic resection. Intraoperative bleeding is increased; the incidence of postoperative liver failure is also increased because of lack of functional reserve. Hepatic regeneration is markedly impaired and reported cures for malignant tumors are rare in cirrhotic patients.

Anatomic Basis for Hepatic Resection

The liver is divided into two lobes, or hemilivers, by the main portal fissure or scissura (Cantlie's line). This line extends from the anteroinferior gallbladder fossa pos-



FIGS. 1A and B. (A) CT scan showing multiple abscesses involving the right lobe of the liver. (From Gutierrez OH, Schwartz SI. Atlas of Hepatic Tumors and Focal Lesions. New York: McGraw Hill, 1984, p. 125, with permission.) (B) The specimen showing multiple abscesses in the right lobe of the liver; this was of biliary tract origin. (From Gutierrez OH, Schwartz SI. Atlas of Hepatic Tumors and Focal Lesions. New York: McGraw Hill, 1984, p. 127, with permission.)

terosuperiorly to the left side of the inferior vena cava. The organization of the right and left lobes or hemilivers is similar. On either side of the main portal fissure there is a right or left paramedian sector. Lateral to each of these is a variable fissure lateral to which is a right or left lateral sector. The left lobe consists of the hepatic tissue to the left of the falciform ligament plus the quadrate and caudate lobes, as they were called in the previous nomenclature.

The right portal fissure divides the right lobe into an anteromedial and posterolateral sector. The right hepatic vein courses along this fissure. The left portal fissure, in which the left hepatic vein courses, divides the left lobe into an anterior and posterior sector.

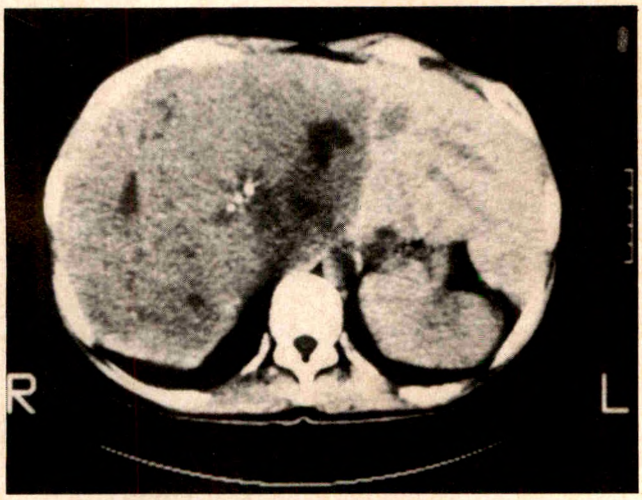


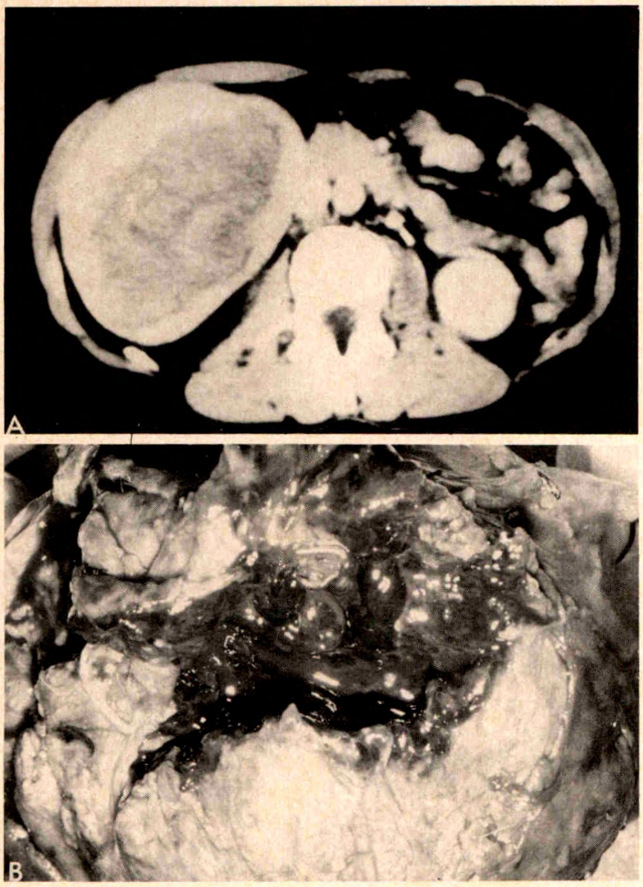
FIG. 2. Hemangioma of the liver involving the entire right lobe and the medial segment of the left lobe. This was removed by trisegmentectomy.

The liver is further divided into eight segments, which are the smallest anatomic units. In the right and left lobes, each of the two sectors is divided into two segments; the anteromedial sector is divided into segment V anteriorly and segment VIII posteriorly. The posterolateral sector is divided into segment VI anteriorly and segment VII posteriorly. In the left lobe, the anterior sector is divided by the umbilical fissure into segment IV, the anterior part of the quadrate lobe, and segment III, which is the anterior part of the left lobe. The posterior sector is comprised only of segment II. The Spigelian lobe, or segment I, is an autonomous segment, with vascularization independent of portal division and the hepatic veins.[26]

As a consequence of these anatomic divisions, a nomenclature for hepatic resection has been established. Two classifications, that of Couinaud[4] and the more commonly applied nomenclature of Goldsmith and Woodburne,[29] are used for the four major resections (Table 1; Fig. 4).

Unisegmentectomy is not applicable for segment I because access to this segment requires preliminary removal of segments II and III. There is little advantage to removing either segment II or III independently because they can be removed together easily as a left lateral segmentectomy. Segmentectomy IV usual refers to excision of the anterior part of that segment. Resection of segment VI alone is rarely performed. Segment VIII resection is difficult because it is connected with the intrahepatic vena cava and segment I.

Plurisegmentectomy of VI and VII may be called right lateral sectorectomy. Bisegmentectomy IV and V is used



FIGS. 3A and B. (A) CT scan of hepatic adenoma with evidence of intratumoral bleeding. (B) Specimen demonstrating lesion with intratumoral clot.

for patients with carcinoma of the gallbladder extending into the liver or for Klatskin tumor. Segments IV, V, and VI may be removed as a unit.

TABLE 1. *Comparison of Classification of Hepatic Resection: Goldsmith and Woodburne* Versus *Couinaud*

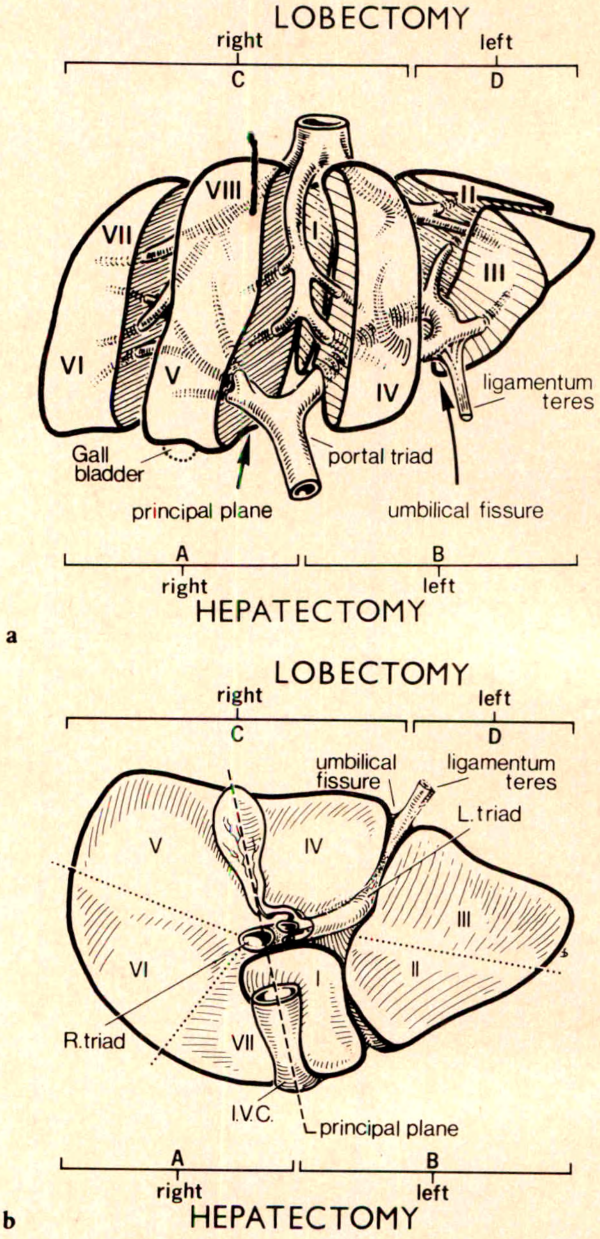
Goldsmith and Woodburne

- Right hepatic lobectomy
- Extended right lobectomy (trisegmentectomy)
- Left hepatic lobectomy
- Left lateral segmentectomy

Couinaud

- Right hepatectomy
  (segments V, VII, VII, VIII)
- Right lobectomy
  (segments IV, V, VI, VII, VIII, ± I)
- Left hepatectomy
  (segments II, III, IV)
- Left lobectomy
  (segments II, III)

Adapted from Blumgart LH. Liver resection—liver and biliary tumours. Chapter 97. *In* Blumgart LH, ed. Surgery of the Liver and Biliary Tract. New York: Churchill Livingstone, 1988, with permission.



FIGS. 4A and B. (A) Exploded view showing the sectors of the liver. (B) Inferior surface of the liver. Segment VIII is not seen because it lies superiorly. (From Blumgart LH. Liver resection—liver and biliary tumors. *In* Blumgart LH. Surgery of the Liver and Biliary Tract. New York: Churchill Livingstone, 1988, p. 1252, with permission.)

Operative Techniques

Resection of a major anatomic portion (Fig. 5) of the liver incorporates several basic features: mobilization, temporary or permanent occlusion of the inflow vessels, transection of the hepatic parenchyma, ligation of intrahepatic vessels and ducts, control of the hepatic veins, and hemostasis of the remaining raw surface.

Mobilization frees the lobe to be resected so it can be delivered into the wound. The ligamentum teres is tran-

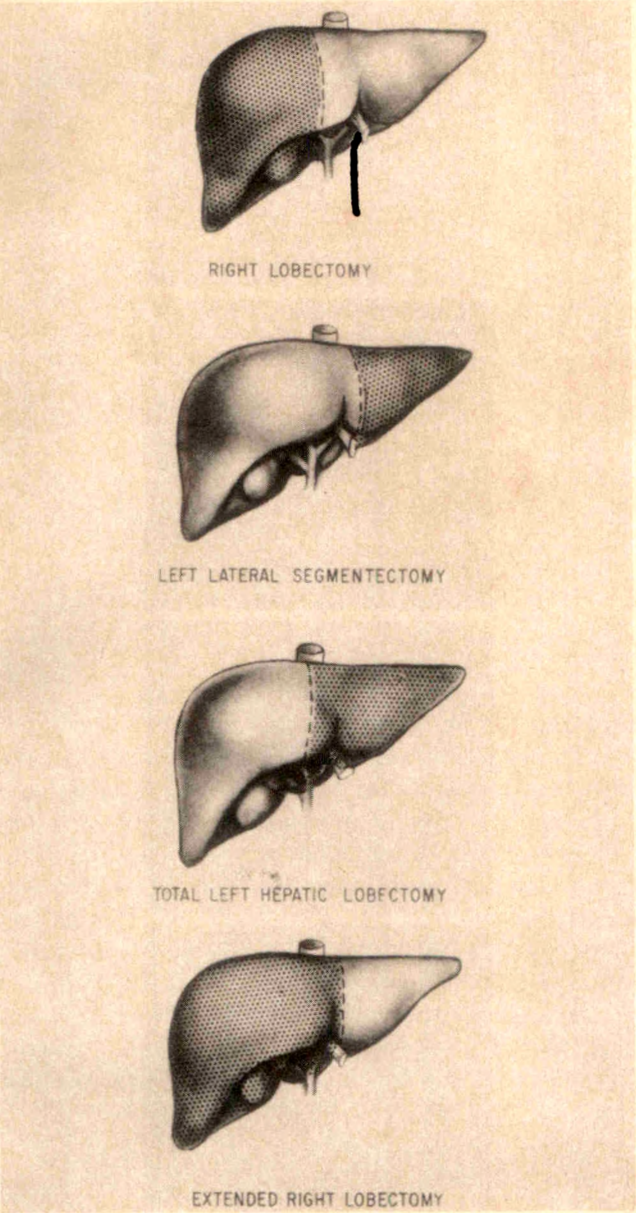


FIG. 5. Nomenclature for hepatic resection. (From Schwartz SI. Liver. *In* Schwartz SI, Shires GT, Spencer FC, and Storer EH. Principles of Surgery. New York: McGraw Hill, 1984, p. 1276, with permission.)

sected and the falciform ligament is divided to a point adjacent to the inferior vena cava. The triangular ligament supporting the lobe to be excised is divided and the dissection is continued by transecting the anterior and posterior coronary ligaments until the suprahepatic vena cava is exposed (Fig. 6).

There are two techniques for right or left lobectomy. The first incorporates individual ligation of the structures in the hepatoduodenal ligament supplying the lobe to be removed and ligation of the hepatic vein draining the lobe before transecting the parenchyma. The advantage of this approach is reduction of intraoperative bleeding and demarkation of the devascularized portion to be removed. The disadvantages are the potential for injury to the inferior vena cava during dissection of the hepatic veins.

The second technique begins with anteroinferior transection of the parenchyma in the plane of lobar division. Before this temporary inflow occlusion can be affected by an atraumatic clamp or an occluding loop incorporating all structures within the hepatoduodenal ligament. Inflow vascular occlusion can be continued for up to 60 minutes without impairing liver function permanently.[30]

The portal elements are ligated and divided as they traverse the plane of dissection within the liver. Dissection is continued posterosuperiorly toward the inferior vena cava. The hepatic vein draining the lobe to be removed is isolated, ligated, and divided, or the vein is preferentially divided between clamps and oversewn within the parenchyma.

This technique reduces operative time, removes an amount of liver tissue specifically related to tumor size and location, and avoids erroneous ligation of vessels providing inflow or outflow for the portion of liver to be preserved. The disadvantage of this approach is that intraoperative bleeding may be greater than with the other technique. I usually use this technique, endorsed by Bismuth, for lobectomy (Fig. 7);[31] for resection of the right lobe, plus the medial sector of the left lobe (trisegmentectomy), the left hepatic artery and portal vein should be skeletonized to allow individual ligation and division of branches to the caudate lobe and feedback vessels to the medical sector of the left lobe.

Technical Refinements

A variety of technical innovations has been applied to hepatic resection. These are generally directed at reducing the extent of bleeding associated with transection of the parenchyma. There are three categories of refinements: (1) improved compression of parenchyma to effect tamponade during dissection; (2) methods of dissection to skeletonize intraparenchymal vessels and; (3) control of bleeding from the raw surface.

In the category of parenchymal compression, several devices have been applied. The first modern report describing a clamp specifically designed for this purpose appeared in 1971. Storm and Longmire[32] reported that their clamp provided uniform pressure on hepatic tissue, and that it significantly reduced the time required to perform a hepatic lobectomy. In his 1973 article, Lin reported that he had designed a special hepatic clamp that made hepatic transection without preliminary inflow or outflow occlusion "almost bloodless."[33] More recently Goldwasser et al.[34] described a new clamp for hepatic resection. The clamp is made of two parallel arms consisting of blunt

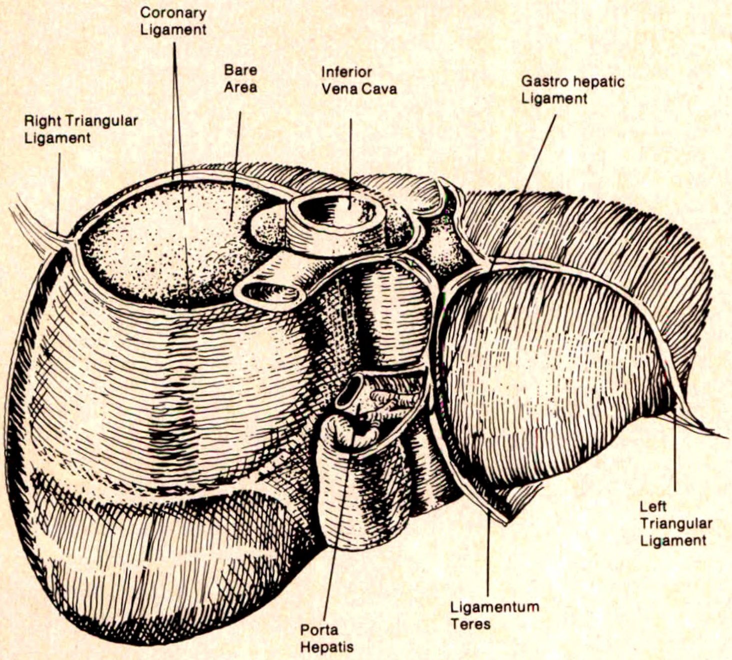


FIG. 6. Ligamentous attachments of the liver. (From Schwartz SI. The liver. *In* Abdominal Surgery. Mt. Kisco, NY: Futura Publishers, 1981. Figure 4, pp. 10–6, with permission.)

cylindrical teeth. The crushing action provided by the teeth leaves the blood vessels and bile ducts that course along the line of resection exposed. Lee and Kim[35] effected compression with a plastic band and locking device (Insulok TR/50L) that was readily applied. It is especially appropriate when the lesion is peripheral. This is a simplification of the first instrument devised to control the hepatic parenchyma by direct compression.[36] The ultimate modification provides permanent compression by a series of interlocking through-and-through sutures placed by means of teeth in a comblike device (Fig. 8).[37] My inclination is not to incorporate any compressive instrument during hepatic resection and, if necessary, to have the first assistant apply pressure to the hepatic parenchyma parallel to the line of dissection.

A variety of approaches has been introduced as a substitute for finger fracture of the parenchyma. In 1974 Almersjö and Hafström[38] described a suction knife to facilitate parenchymal transection. In 1984 Hodgson and DelGuercio[39] reported their experience with the ultrasonic dissector (CUSA™ system, Cavitron, Inc., Stanford, CT) to disrupt liver parenchyma and isolate traversing vessels and ducts. The system provides fragmentation of tissue, irrigation, and aspiration of the fragments. The instrument

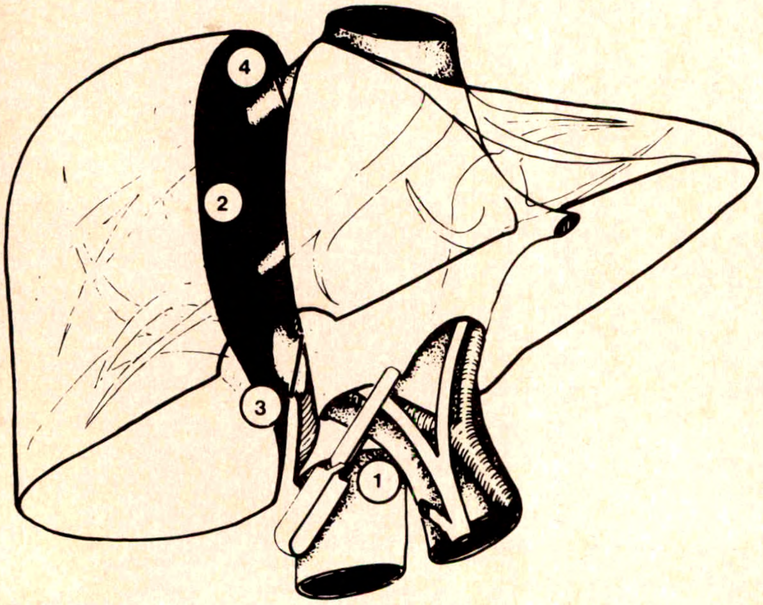
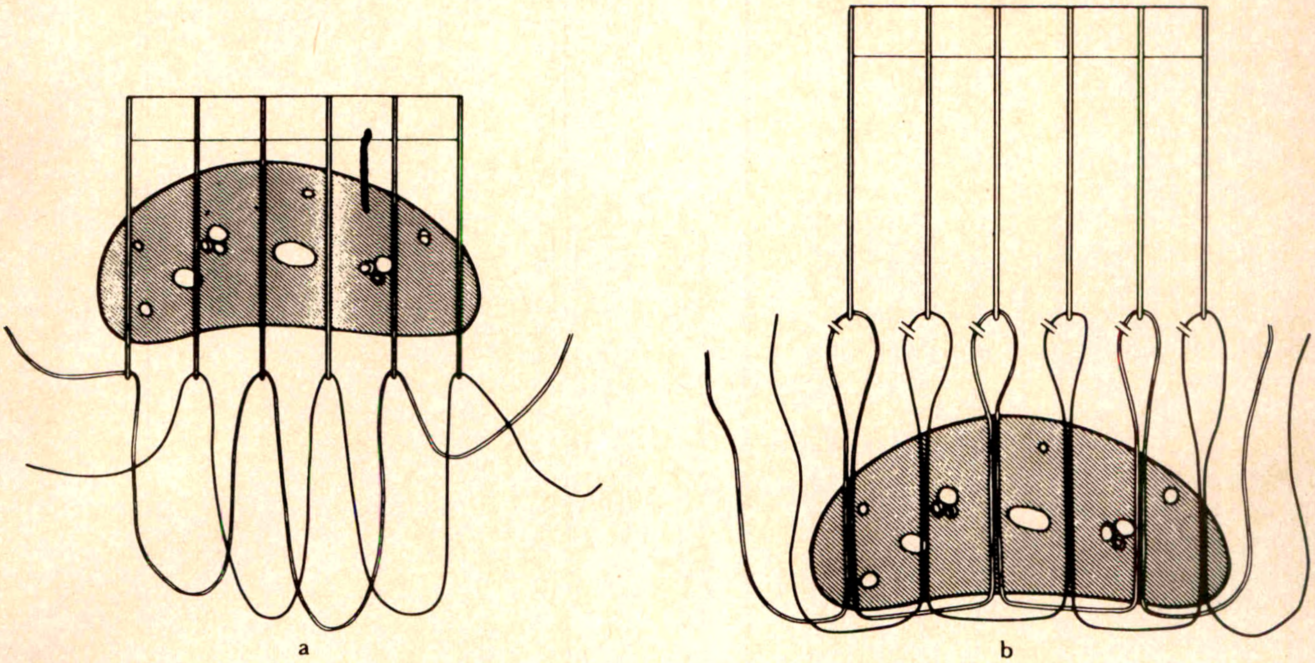
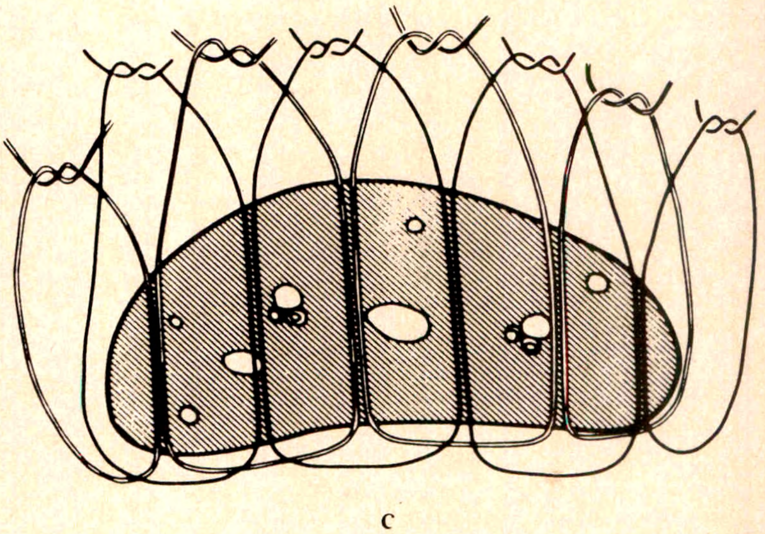


FIG. 7. Sequence of events: (1) temporary occlusion of structures in hepatoduodenal ligation, (2) anterior parenchymal dissection, (3) parenchymal dissection of portal structures, and (4) parenchymal dissection of hepatic vein. (From Bismuth H. Surgical anatomy and anatomical surgery of the liver. World J Surg 1982; 6:3, with permission.)





FIGS. 8A–C. (A) Two long sutures are threaded through the holes at the tip of the needles; (B) the comb is pulled out and the sutures are cut in several places; and (C) each suture is tied with caution to avoid tearing the liver tissue. (From Nagao T, Kawano N, Morioka Y. A new instrument for hepatic resection. Surg Gynecol Obstet 1988; 166:270; Fig. 3, with permission.)

should be set at 80% to 90% of full power during the dissection until larger vessels are approached, at which time the power should be reduced to 70%. The ultrasonic device is a dissector and provides no hemostasis in itself. A specially designed water jet has been used to fragment and wash away parenchymal tissue, leaving ducts and vessels to be ligated.[40] The system is an inexpensive variation of ultrasonic dissection.

Lasers combine dissection and hemostasis. The hemostatic property is related to formation of a thin coagulum on the surface. In the case of the CO_2 laser, this is only 0.05 mm thick.[41] The Nd-Yag laser offers a theoretic advantage, but one study showed that ultrasonic dissection was superior to the noncontact Nd-Yag laser method and finger fracture when measuring tissue damage.[42] In contrast another group reported that the ultrasonic dissector and contact Nd-Yag laser were not significantly better than the suction knife in performing major resections when operating time, blood loss, and postoperative liver function were assessed.[43]

My preference is the finger fracture approach because I am familiar with that technique, and because it minimizes the time of parenchymal transection. I use the ultrasonic dissector on occasion for a trisegmentomy or for excision of a large central hemangioma with multiple contributing vessels. I have no experience with laser dissection of the liver.

Diffuse oozing from the remaining raw surface of the transected liver can usually be controlled by temporarily applying direct pressure or a local hemostatic agent (such as oxydized cellulose or micronized collagen). Glues and adhesive sprays have been used but have been too inflammatory. A saphir infrared device has been used to produce hemostasis on the surface. Microwave application to the raw surface to induce a 2-to-3-mm deep coagulation is being evaluated.

In addition to the three categories that have been discussed, real-time operative ultrasonography has reduced operative bleeding. Although the procedure was introduced to define the extent and multiplicity of tumors, it provides a mapping of the major intrahepatic portal and hepatic venous vessels. This aids in guiding the line of transection and thereby reduces blood loss.[43,44]

As a consequence of better understanding the liver anatomy and the development of effective operative techniques, hepatic resection is now associated with acceptably low mortality and morbidity rates when it is performed by experienced surgeons. This has led to a broadening of indications for resection. Continued concern for intraoperative bleeding during parenchymal transection has stimulated refinements of technique and instrumentation, but the advantages of these refinements have not yet been documented.

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Gastrinoma Excision for Cure

A Prospective Analysis

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The role of surgery in the treatment of gastrinoma is unclear. The purpose of this study was to determine prospectively the surgical cure rate using a controlled clinical trial. Eleven patients who fit the entry criteria underwent abdominal exploration and attempted tumor resection for cure. A historical control group was used for comparison. Cure was defined as: (1) normal serum gastrin level, (2) no response to intravenous secretin, (3) no symptoms when antisecretory medications are stopped, and (4) no tumor recurrence on follow-up examination. Tumors found in both groups tended to be small (1.5 cm *vs.* 2.2 cm), multiple (71% *vs.* 40%), and in lymph nodes (70% *vs.* 70%). All tumors identified were located anatomically within the gastrinoma triangle. Tumors were found in 10 of 11 patients (91%) in the study group, and significantly more patients had their tumors excised for cure as compared to controls (82% *vs.* 27%, $p < 0.05$). The current prospective cure rate for gastrinoma is higher than previously appreciated and tumors within lymph nodes do not preclude curative resection.

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THE ROLE OF SURGERY in the treatment of gastrinoma remains unclear.[1-5] Optimal therapy would be complete surgical excision of the tumor to alleviate gastric acid hypersecretion, as well as to prevent tumor progression. Historically it was believed that tumor excision for cure was possible in only 2% to 5% of patients.[4] Therefore therapy was directed primarily at controlling gastric acid hypersecretion with H_2-antagonists or total gastrectomy. Recently, however, a number of scientific advances have improved our ability to successfully remove gastrinoma for cure. They are the gastrin radioimmunoassay (RIA),[6] perioperative acid control,[7] improved patient selection,[8] knowledge of tumor location,[9] and information on the clinical course of patients with tumors within lymph nodes.[10]

As a result of the gastrin RIA, patients are now seen earlier with resectable tumors.[11] Perioperative control of gastric acid hypersecretion with H_2-receptor antagonists has allowed safer explorations and more aggressive attempts at tumor resection.[12] Intraoperative identification of small or occult tumors has been facilitated by the recognition that most gastrinomas are located in a specific anatomic area called the gastrinoma triangle.[9] Now that a number of investigators have reported long-term cures resulting from the excision of these tumors, patients with tumors in lymph nodes are potential candidates for cure.[8,10,13-16] In contrast patients with hepatic metastases or multiple endocrine neoplasia type I syndrome (MEN I) are unlikely to have complete tumor excision and are therefore not candidates for cure.[17]

Collectively these advances have profoundly influenced the ability to successfully resect gastrinomas for cure. Clinical data to support this assertion is found in the results of several recently reported series in which the collective cure rate was 32%.[8,18,19] To investigate the surgical cure rate prospectively, we began a controlled clinical trial in 1982 in which appropriate candidates had abdominal exploration solely to identify intraoperative tumors and excise for cure.

Patients and Methods

From August 1982 to October 1988, 15 consecutive patients were evaluated for excision of gastrinoma for cure. There were nine men and six women, with a mean age of 49 years (range, 32 to 72 years). The diagnosis of gastrinoma was made in all 15 patients based on clinical evidence of severe peptic ulcer disease, fasting serum hypergastrinemia (> 200 pg/mL), and increased serum gastrin (> 200 pg/mL) when secretin was administered intravenously.

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The criteria used for candidate selection was (1) sporadic gastrinoma without associated MEN I syndrome, (2) no preoperative evidence of hepatic metastases, and (3) acceptable surgical risk for abdominal exploration. Screening for MEN I syndrome was performed by obtaining a thorough family history and measurement of serum calcium, phosphate, and parathyroid hormone levels. In any uncertain case, a serum prolactin assay was also performed. All patients were screened before operation for evidence of hepatic metastases by abdominal CT scan.

Using the above criteria, of the 15 patients seen, two had MEN I syndrome and two had hepatic metastases, which left 11 patients for study. After informed consent, all patients underwent laparotomy, abdominal exploration, and tumor excision as previously described.[9] An extensive and diligent search for tumors was performed, concentrating the dissection in the area of the gastrinoma triangle. Whether a primary tumor in the pancreas or duodenum was found, all lymph nodes identified within the gastrinoma triangle were excised and submitted for histologic examination. This was done to identify occult lymph node disease. If tumors were identified only within lymph nodes, with no evidence of primary disease after exhaustive exploration, patients were closed and continued on H2-antagonists until the results of serum gastrin and secretin tests were known. No major pancreatic or gastric resection was performed. Surgical cure was defined as (1) normal serum gastrin level, (2) no responsive to intravenous secretin, (3) no symptoms when antisecretory medications were stopped, and (4) no tumor recurrence on follow-up examination.

The current analysis is based on follow-up observations through November 1, 1988. Each patient had a postoperative secretin test within 2 months of discharge. If the results were negative, antisecretory medications were stopped and the patients were followed. Eight of 11 have been continuously followed at 6-to-12 month intervals for periods of 2 to 72 months with physical exams, serum gastrin determination, and secretin tests at approximately 6-month intervals.

For comparison, an external historical control group consisting of consecutive patients seen by the authors between 1974 and 1981 was used. Each patient seen during this time period was evaluated for entry into this study using the same criteria that was applied to the prospective group described above. Consecutive patients were evaluated to minimize selection bias. The years 1974 to 1981 were used because these patients were seen in the period immediately before the initiation of this study and after the introduction of the gastrin RIA.

Nineteen patients were seen during this time period; five patients with MEN I syndrome and three patients with hepatic metastases, which left 11 patients in the control group for analysis. All patients had laparotomies and tumor resection was attempted. During this time period, 10 patients also had a total gastrectomy in addition to attempted tumor removal. Postoperative follow-up was similar to that described for the study group above. In all, seven patients have been followed continuously for 84 to 168 months, two patients died after 12 and 32 months of follow-up, and two patients were lost to follow-up after 48 and 24 months.

Statistical analysis was performed using the chi square, two-sided Fischer's exact test, or the unpaired Student's t test. Significance was defined as $p < 0.05$.

Results

Patient characteristics between the control group and the study group are given in Table 1. The patients in the two groups were similar in age, sex, and average duration of symptoms before diagnosis. Complications due to peptic ulcer disease (upper GI bleeding greater than two units, perforation, or obstruction/stricture) were common in both groups before operation for attempted tumor removal (100% *vs.* 73%). The types of complications seen were similar in both groups with upper GI bleeding occurring most often.

The two groups differ significantly in the timing of their complications in relation to diagnosis. All of the complications in the control group (11 of 11 subjects) occurred before the diagnosis of gastrinoma was made. In this group the presence of a severe ulcer complication usually prompted the initial evaluation of the Zollinger–Ellison syndrome. In the study group, however, five of the seven complications (four bleeding, one obstruction) occurred after the diagnosis of gastrinoma was made. In addition, at the time of their complication, all five patients were taking a H$_2$-receptorantagonist.

TABLE 1. *Clinical Characteristics of the Control and Study Groups*

Characteristic	Historic Control 1974–1981 (N = 11)	Study Group 1982–1988 (N = 11)	p value
Age, mean + SD (yrs.)	49 ± 11	50 ± 11	NS†
Sex			
Male	9 (82)‡	7 (64)	NS
Symptom duration (yrs.)	7 ± 4	6 ± 5	NS
Previous operations	6 (55)	3 (27)	NS
Ulcer complications	11 (100)	8 (73)	
Bleeding	9	7	NS
Obstruction	1	1	NS
Perforation	1	0	NS
Before Tx.§	11	2	*p < 0.01
After Tx.	0	6	*p < 0.02

* Two-sided Fischer's exact test.

† NS, not significant.

‡ Percentages shown in parentheses.

§ Tx., treatment.

The major indication for surgical referral in nine of ten patients in the study group was endoscopic evidence of persistent duodenal ulceration (seven patients), esophageal inflammation (one patient), or esophageal stricture (one patient), despite treatment with a variety of H_2-receptor antagonists. Objective evidence of persistent ulceration/ and or inflammation was present in five of these patients, despite a subjective improvement in symptoms.

Tumors were located at laparotomy in 91% (10 of 11) of patients in the study group. In contrast tumors were found in only 64% (7 of 11) of patients in the control group. All 24 tumors found in both groups of patients were within the anatomic boundaries of the gastrinoma triangle. The location of tumors removed from patients in the study group are depicted in Figure 1.

The characteristics of the tumors found in both groups were similar (Table 2). The mean tumor size ([control] 1.5 cm + 1.3 cm, *vs.* [study] 2.2 cm + 1.7 cm), incidence of multiple tumors (45% *vs.* 40%), occurrence of tumors in extrapancreatic/extraintestinal sites (14% *vs.* 36%), and occurrence of tumors within lymph nodes (71% *vs.* 70%) were not different for the groups. Primary nodal tumors (*i.e.*, without detection of a corresponding primary tumor) were found and excised in one patient in the control group and in four patients in the treatment group (Table 3).

The surgical cure rate was significantly higher for patients in the study group (27% *vs.* 82%, $p < 0.05$). Interestingly the excision of primary nodal tumors resulted in the cure of one patient in the control group (follow-up, 84 months), and in three of four patients in the prospective treatment group (median follow-up, 12 months). The median follow-up was significantly longer for the control group when compared to the study group (120 months *vs.* 9 months, $p < 0.01$).

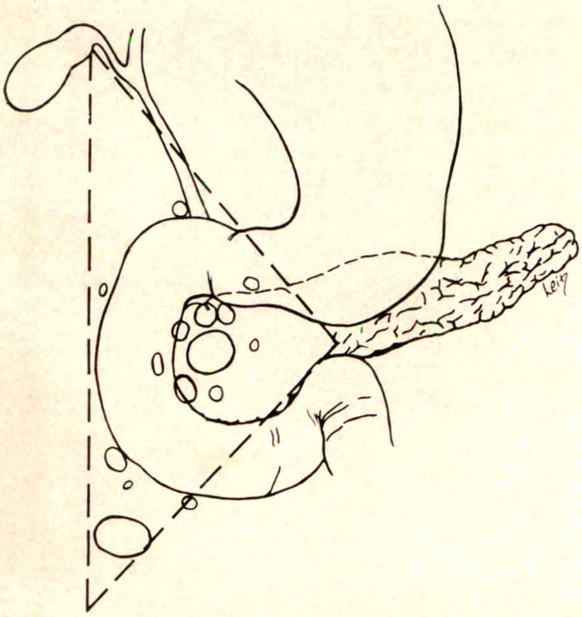

FIG. 1. Intra-abdominal location of 16 tumors found in ten patients in the study group.

TABLE 2. *Tumors Found in Patients Explored for Gastrinoma*

	Historic Control 1974–1981 (N = 11)	Study Group 1982–1988 (N = 11)
Patients with + exploration	7 (64)†	10 (91)
Pancreatic	4	3
Duodenal	2	3
Extra/extra*	1	4
Patients with multiple tumors	5 (71)	4 (40)
Total tumors found	13	16
Mean size of tumors (cm ± SEM)	1.5 ± 1.3	2.2 ± 1.7

* Extra/extra, extrapancreatic/extraintestinal tumors.
Percentages shown in parentheses.

Because a total gastrectomy was performed in 10 of 11 patients in the control group, morbidity and mortality rates could not be compared directly. It is for this reason that operative complications were evaluated for the study group only. Three related complications occurred in one patient in the study group, resulting in an overall morbidity rate of 10%. There were no reoperations or perioperative deaths. Complications occurred in a 71-year-old man and included a perioperative subendocardial myocardial infarction, renal insufficiency, and a prolonged postoperative ileus. All complications responded to conservative management and recovery was complete.

Discussion

Surgical cure rates reported for gastrinoma excision have gradually improved.[17] Conventional teaching was that surgical cure rates were in the range of 2% to 5%,[4] and cure was believed to be theoretically impossible in 80% of patients.[20] As a result of this perception, medical treatment with H_2-receptor antagonists has been advocated as the initial form of therapy until either medical treatment fails or the patient develops a life-threatening complication. The ideal treatment of gastrinoma is still surgical excision of the tumor if this can be accomplished

TABLE 3. *Characteristics of Lymph-Node Tumors Found in Patients with Gastrinoma*

Characteristic	Historic Control 1974–1981 (n = 11)	Study Group 1982–1988 (n = 11)
Patients with lymph-node tumor	5 (45)*	7 (64)
Solitary	1	4
Occult	3	2
Multiple	1	1
Total lymph-node tumors	6	9

* Percentages shown in parentheses.

with a high probability of success and low risks of morbidity and mortality.

In this study we reported on 11 patients who we considered candidates for surgical cure. These patients were matched with 11 patients derived from the authors' own series who were seen from 1974 to 1981. The limitations of comparison between these two groups is well recognized.[21] Nevertheless, considering the rarity of this tumor, the limited experience accrued by any one practitioner, and the methodologic problems in multi-institutional clinical study, a prospective randomized trial seems unlikely. We believe such a comparison seems reasonable and, for now, is the best alternative available.

In terms of the therapeutic philosophy prevalent in the two different time periods studied, it is interesting to note that in contrast to the control group, all peptic ulcer complications in the study group occurred after the diagnosis of gastrinoma had been made. In fact 75% of these complications occurred while the patients were on histamine H_2-receptor antagonists. Although the authors were not following the patients at this time, the available information indicates that all six patients were compliant, took their medication as prescribed, and were asymptomatic at the time the complication occurred (Table 4). Therapy was ongoing for 11 to 60 months before their complications. It has been well documented that merely assessing subjective symptoms is unreliable in predicting the efficacy of H_2-receptor antagonists therapy in this group of patients.[21] Because of this fact, four of the six patients (67%) were followed at 3-to-6 month intervals by routine endoscopy. In all four of these patients persistent ulceration and inflammation was found. Doses of medication were increased in three of the four patients and bethanecol was added to the regimen of the fourth. Despite these adjustments, complications still occurred. Clearly the main criticism of this finding is that the dosages of medications given to these patients were inadequate to control the gastric hypersecretion in patients with gastrinoma. While the dosages given in this study are large in comparison to patients with peptic ulcer disease, they were considerably lower than the mean dose of cimetidine (4.6 g/day) or its equivalent given at the National Institutes of Health (NIH).[2] Therefore, based on this data, no definitive conclusions can be drawn with regard to the overall efficacy of histamine H_2-receptor antagonists in the treatment of gastrinoma. It can be stated, however, that the dosages given in this series were inadequate to control the peptic ulcer complications in this group of patients, and routine endoscopy does not preclude therapeutic failure.

TABLE 4. *Patients in Study Group Who Had Complications While on H_2-Receptor Antagonist Therapy*

Patient	Medication	Dosage (g/day)	Complication	Length of Tx.* (months)
1	Cimetidine	2.4	Bleeding	36
2	Cimetidine	1.2	Bleeding	11
5	Ranitidine	.9	Esophageal stricture	12
6	Cimetidine	2.4	Bleeding	60
8	Cimetidine	1.2	Bleeding	12
9	Famotidine	.12	Obstruction	12

* Tx., treatment.

One of the differences found between the control and study groups is the success of identifying tumors at laparotomy. In the control group, 64% of patients had tumors identified and resected. This value compares favorably with the 41% to 70% rate reported in recent surgical series.[8,18,19,22,23] In contrast 91% of patients in the study group had tumors identified and excised. Although these values are not statistically different, this increased rate of tumor identification is a major factor contributing to the improved surgical cure rate. Possible reasons for this increase in tumor identification include better preoperative imaging, changes in operative technique, or increased experience by the operating surgeon (learning curve).

Although preoperative localization (CT scan) was not available in the control group, its impact on tumor identification in the study group was minimal. In this study preoperative CT scanning had a 30% sensitivity (3 of 10 patients) and 100% specificity. These results are comparable to the early reports on CT localization in the literature but they are much lower than the recently reported series in which a sensitivity rate of 59% to 78% was found.[24-26] There are several variables in our CT data that may explain this discrepancy. Although all patients who underwent CT scanning in our study had both oral and intravenous contrast, we do not routinely give the bolus intravenous contrast infusion technique as described by Stark et al.[26] This may decrease our sensitivity in tumor localization by diminishing the vascular blush seen with tumors in their series. In addition, in contrast to the studies previously mentioned, the CT scans in our series were interpreted by different staff radiologists at several UCLA-affiliated hospitals in which the patients were seen. Consequently we did not have the benefit of a single radiologist who interpreted all the scans. Perhaps the most important variable, however, is the size and location of tumors found in our study. It has been shown that the ability of CT to identify tumors is directly related to the tumor size (0% at a size of less than 1 cm *vs.* 83% to 95% at a size of more than 3 cm) and tumor location (pancreatic 80% *vs.* extrapancreatic 35%).[25] Three patients in this study had tumors measuring 1 cm or less in diameter and seven patients had tumors in extrapancreatic locations. Viewed in this context, our sensitivity for CT scanning is consistent with that reported in the literature.

It should be noted, however, that of the three patients with positive CT scans, two patients had multiple tumors

TABLE 5. *Patients in Study Group Who Underwent Attempted Excision of Gastrinoma for Surgical Cure*

Patient	Age	Sex	Tumor Location	Preop. Gastrin (pg/mL)	Postop. Gastrin (pg/mL)	Postop. Secretin Test	Follow-up (months)
1	33	M	Triangle*	3858	84	−	72
2	54	M	Triangle	176	74	−	37
3	49	F	Triangle	1100	99	−	15
4	40	M	Triangle	196	55	−	12
5	59	F	Triangle	1568	88	−	11
6	59	M	Triangle	190	46	−	9
7	49	M	Triangle	3131	434	+	7
8	65	F	Triangle	2605	95	−	7
9	71	M	Triangle	1428	74	−	6
10	56	F	Triangle	5494	63	−	2
11	55	M	Not found	1100	875	+	1

* Within the gastrinoma triangle.

(four tumors in total), of which only one was identified on CT scan before operation. All of these tumors were occult within lymph nodes and could only be identified by frozen section histology. Furthermore resection of a tumor visualized on CT without careful intraoperative exploration would have resulted in a number of occult tumors being missed. Therefore, although CT scans are useful in the preoperative evaluation of hepatic metastases and may provide evidence of tumor location in up to 78% of patients, its role seems limited in actual tumor identification.

When analyzing the types of tumors present in this series, of particular interest is the small average size, incidence of extrapancreatic tumors, and the number of tumors within lymph nodes found in both groups of patients.

The average tumor size is comparable between groups and is consistent with the average sizes recently reported in the literature.[8,19] Extrapancreatic and duodenal gastrinomas are believed to be a subgroup of patients with gastrinoma that have a favorable cure rate.[14–16] In addition some studies have suggested that because of the introduction of the gastrin RIA, the incidence of this type of gastrinoma is increasing.[11,18,23] In this study 43% of the control group and 70% of the study group had tumors in this location. The increased incidence of these tumors in the study group, although again not statistically different, is another factor that contributes to the observed differences in cure rate. Although early surgical series reported a low incidence of these tumors,[27,28] recent reports confirm our finding that a larger percentage of tumors are now found in these locations.[8,19] If this observation is correct, it suggests that gastrinomas may now be more amenable to cure. Some investigators have cited the gastrin radioimmunoassay and earlier diagnosis as the reason for this apparent shift in location, although the data is unclear.[11,23]

Extrapancreatic/extraintestinal tumors were found in one patient in the control group (14%) and in four patients (40%) in the study group. Of these five patients, all had primary nodal tumors located in the peripancreatic region. There was no associated pancreatic or duodenal tumors found in these patients. Of these five patients, four are surgical cures with a median follow-up of 14 months (range, 2 to 84 months). This high incidence of isolated lymph node involvement in any one series is unusual; however a number of authors have reported similar success in excising primary nodal gastrinomas for cure.[8,10,14–16] In the majority of previous reports, however, most patients also had a concomitant total gastrectomy. One of the criticisms of these early reports is that a small undetected primary tumor in the surgical specimen could not be ruled out entirely. Three out of the four patients in this series who were surgical cures had no other resection performed besides lymph-node removal. This experience supports the existence of isolated aberrant primary gastrinoma within lymph nodes.[10]

Operative technique and the surgeon's experience are both uncontrolled factors in this study in terms of the ability to locate tumors at laparotomy. From a technical standpoint, the major differences between the two patient populations and time periods studied were the thorough dissection and extensive tissue sampling carried out in the area of the gastrinoma triangle in patients in the study group. The gastrinoma triangle is defined as the junction of the cystic duct and common bile duct superiorly, the second and third portions of the duodenum inferiorly, and the junction between the neck and body of the pancreas medially.[9] As pointed out before, many of these tumors were small, multiple, and occult within lymph nodes. Although difficult to quantitate experimentally, we believe that careful dissection, palpation, and lymph node sampling in this area has improved our ability to localize tumors during operation and resect them for cure.

The surgical cure rate for the study group was 82% and that in the control group was 27% ($p < 0.05$). Contributing factors, as mentioned previously, include improved tumor identification, increased surgical experience, and a increased percentage of extrapancreatic tumors. All patients in this series who are considered cures are followed clinically off antisecretory medications and with periodic serum gastrin levels and secretin tests (Table 5). In the analysis of this data, the relatively short follow-up (9 months, range 2 to 74 months) in the treatment group is an area of contention. Some series report a failure rate as high as 42% within the first 6 months.[8] In our experience we have yet to see a patient with sporadic gastrinoma after successful resection and a negative postoperative secretin test develop other tumors. Unlike other malignancies, gastrinoma has a very sensitive and specific serum marker, namely the stimulation with secretin to detect primary and recurrent tumors.[29] Imaging studies, *i.e.*, ultrasound, CT scan, or angiogram, are not cost-effective for routine postoperative surveillance for recurrent tumors unless the patient has biochemical evidence of disease, *i.e.*, elevated serum gastrin or positive secretin test. Therefore, even with a relatively short follow-up (median, 9 months), based on the biochemical profiles of our patients, we believe this data is meaningful.

The clinical expression of gastrinoma has changed markedly since the early reports on surgical experience with this tumor. In selected patients a meticulous abdominal exploration and lymph node sampling in a specific anatomic area will result in an excellent rate of intraoperative tumor identification. When tumors are identified and excised, even if present as isolated tumors within lymph nodes, the surgical cure rate can be as high as 82% at a median follow-up of 9 months. These results can be accomplished without major pancreatic or gastric resection, and with an acceptable morbidity rate (10%) and no surgical deaths. The current prospective surgical cure rate for gastrinoma is higher than previously appreciated. Abdominal exploration and surgical excision of gastrinoma for cure is the optimal treatment for this group of patients.

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Acute Gastroduodenal Perforations Associated with Use of Crack

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Crack, the free-base form of cocaine, was introduced as an illicit street drug in 1986. Since then, we have noted a significant increase in acute gastroduodenal perforations. Between 1982 and 1986, we treated 11 patients with such perforations. This represents a constant occurrence rate of 6% of hospital admissions for peptic ulcer disease. Since 1986 we have treated 16 patients with gastroduodenal perforation, which yields an occurrence rate of 16%. Nine of the 16 patients had a close temporal relationship between the use of crack and the onset of their perforation. This group was younger and disproportionately comprised of male patients. These findings led us to believe that there may be a pathogenic relationship between the use of crack and acute gastroduodenal perforation, and the clinician should be aware of the various potential complications of this new drug. This relationship also raises questions about the exact pathophysiology of peptic ulcer disease.

COCAINE IS AN alkaloid prepared from the leaves of the *Erythroxylon coca* plant. It acts at the synaptic level where it alters neurotransmitter reuptake, potentiating the effects of norepinephrine and dopamine.[1] Crack, the new free-base form of cocaine that has grown in popularity throughout the major metropolitan areas of the United States, is not destroyed by heating and can therefore be effectively administered by smoking. Many well-documented pulmonary, cardiac, obstetric, neurologic, and gastrointestinal complications have been associated with cocaine use.[1–4] The advent of crack as a popular street drug has recently introduced additional complications[5–12] (Table 1). A frequent association between gastroduodenal perforations and a history of crack use seen at our institution during the past 2 years prompted a review of all gastroduodenal perforations since 1982.

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Methods

All hospital admissions for peptic ulcer disease between 1982 and 1988 were reviewed. Twenty-seven consecutive cases of nonmalignant, nontraumatic gastroduodenal perforations were identified and reviewed for age, sex, antecedent drug use, previous medical or surgical treatment of peptic ulcer disease and operative findings, and management of the perforation.

Results

There were 27 cases of gastroduodenal perforations in our institution from 1982 to 1988. In nine cases there was an association with crack use (group I). The remaining 18 patients had no history of crack use (group II). Diagnosis of perforation was based on a combination of careful history, physical examination, marked leukocytosis, and free air under the diaphragm on a chest radiograph.

There were eight men and one woman in group I. They all presented between 1986 and 1988. Their average age was 30 years, ranging from 22 to 48 years. Two of the nine patients had a previous history of peptic ulcer disease. The time interval between the perforation (as suggested by the characteristic acute onset of sharp epigastric pain) and the smoking of crack ranged from one hour to three days (Table 2). All perforations were either juxtapyloric or within the first part of the duodenum. In the two cases with a history of peptic ulcer disease, chronic ulcerations were found. There was gross spillage of gastric contents in all cases, and a pelvic abscess in one. Intraoperative cultures revealed combinations of *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus aeruginosa, Proteus mirabilis,* and *Candida albicans.* All nine patients underwent exploratory laparotomy with Roscoe-Graham omentopexy. There were no perioperative deaths; the av-

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TABLE 1. *Complications of Crack Use*

Author	Complication	Age	Sex
Shesser,[5] 1985	Pneumomediastinum/ pneumothorax	26	F
Shesser,[5] 1985	Pneumothorax	19	F
Patel,[6] 1987	Bronchiolitis obliterans pneumonia	32	M
Murray,[7] 1988	Diffuse alveolar hemorrhage	36	F
Morris,[8] 1985	Pneumomediastinum	21	M
Zamora-Quezada,[11] 1988	Diffuse muscle and skin necrosis	20	F
Androuny,[12] 1985	Pneumopericardium	20	M

TABLE 3. *Characteristics of Patients with Gastroduodenal Perforation*

Characteristic	Group I (crack)	Group II (no crack)
Age (years)	30	44
Sex ratio		
Male (%)	89	61
Female (%)	11	39
History of PUD (%)	22	61
Treatment (%)		
Omentopexy	100	94
Antrectomy/vagotomy		6

PUD, peptic ulcer disease.

erage length of stay was nine days. All patients were placed on H-2 blocker and antacid therapy at time of discharge.

Group II consisted of 18 patients, none of whom gave a history of crack use. The average age for this group was 44 years. The male-to-female ratio was 11:7. Group II patients represent 6% of all patients admitted for peptic ulcer disease, averaging three perforations per year. Eleven patients had a history of peptic ulcer disease, nine of whom were being treated with antacids and H-2 blockers. None of the patients had undergone previous surgery for their disease. All patients underwent immediate abdominal exploration. Roscoe-Graham omentopexy was performed in 17 cases and antrectomy and vagotomy in one. There was one perioperative death in this group. Table 3 summarizes the characteristics of both groups.

Discussion

Within the last 2 years, we have seen a dramatic increase in the incidence of acute gastroduodenal perforations (Fig. 1). Two groups of patients can be distinguished, differing in mean age and male:female ratio. Group II appears to be representative of the general population of patients with a perforated peptic ulcer with regard to incidence, age, and sex distribution. Perforated peptic ulcers account for 5% to 10% percent of all hospital admissions related to peptic ulcer disease.[13-17] Jordan et al.[13] have shown that, despite a decline in the overall incidence of peptic ulcer disease during the past decades, the number of cases of perforated peptic ulcers has not significantly changed. There has been an increase in perforations in the older age group with a shift in peak age from 40 to 49 years.[13] The male-to-female ratio for peptic ulcer disease has declined from 2.2:1 in 1965 to 1.2:1 in 1981.[16]

In contrast to this group of predictable perforations, we have observed the appearance, since 1986, of a rapidly enlarging group of patients (group I) who are relatively younger, almost always male, and who all give a history of crack use closely related to the time of gastroduodenal perforation (Fig. 2). These patients account for the overall increase in incidence of gastroduodenal perforations, from 6% to 16% of all patients admitted for peptic ulcer disease.

Crack, the free-base form of cocaine, is now readily available as a street drug. Although its different form may uncover complications not previously seen, the pharmacologic properties of crack appear to be similar to cocaine,[1] namely an alteration of neurotransmitter reuptake. At the gastrointestinal level, this potentiating effect on norepinephrine results in an intense vasoconstriction secondary to stimulation of alpha-adrenergic receptors in the mesenteric vasculature, leading to focal tissue ischemia and perforation.[1-3] The chronologic relationship of crack use to gastroduodenal perforation leads us to surmise that a possible crack-related ischemic event is the cause of per-

TABLE 2. *Gastroduodenal Perforations Associated with Crack Use*

Age	Sex	History of Crack Use	PUD
26	M	48 hours before	No
33	F	6 hours before	Yes
31	M	8 hours before	No
32	M	8 hours before	No
22	M	4 hours before	No
25	M	24 hours before	No
29	M	8 hours before	No
48	M	60 hours before*	Yes
30	M	1 hour before	No

PUD, peptic ulcer disease.

* Delayed presentation. However perforation is estimated to occur less than 24 hours after crack use.

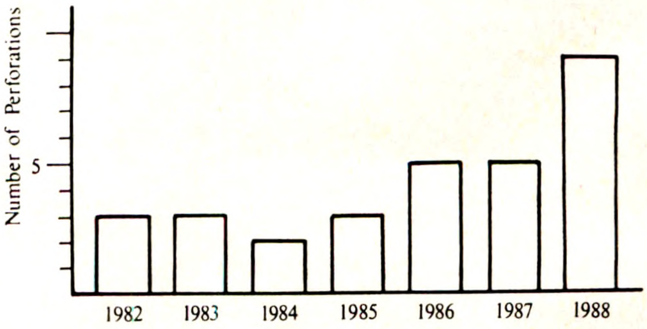

FIG. 1. Incidence of gastroduodenal perforations at St. Mary's hospital, 1982 to 1988.

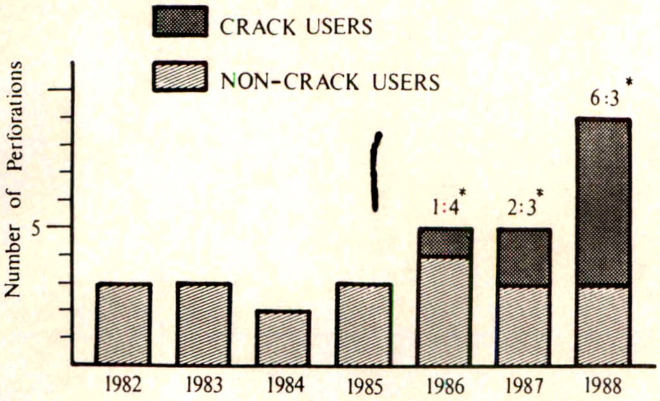

FIG. 2. Incidence of gastroduodenal perforations and its association with the use of crack.
* Crack:No crack ratio.

foration in these patients. For postoperative therapy these patients should probably receive H-2 blockers and/or antacids until it can be clearly demonstrated that they are not at an increased risk for the development of peptic ulcer disease.

We report a preliminary series of nine patients treated at our institution during the past 2 years for acute gastroduodenal perforations chronologically associated with the use of crack. Although the exact pathophysiology is not known, we believe that this new form of cocaine may be contributing to, if not inducing, these perforations. Physicians in urban areas, where this recreational drug is rapidly becoming more popular, should be aware of this and possibly other complications of crack use.

Comment

The relationship of crack use, focal tissue ischemia, and gastroduodenal perforation raises fundamental questions about the etiologies of peptic ulcer disease. One third of the patients who present with an acute gastroduodenal perforation without previous history of peptic ulcer disease will heal completely without further treatment, after surgical management of the acute perforation,[17,18] leaving one to wonder if these patients have a bonafide ulcer diathesis. Indeed they may only have had an acute ischemic episode resulting in the acute perforation.

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Hepatobiliary Cystadenoma with Mesenchymal Stroma

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In a detailed review of cystic hepatobiliary neoplasms, we identified a subset of 50 cases in which tumors were characterized by the presence of a mesenchymal cell layer interposed between an inner epithelial lining and an outer connective tissue layer. We have recently seen three such patients, making a total of 53 patients reported in the English literature. All of the patients were female, 44 of whom, with an average age of 41 years, had benign tumors. The average age of the remaining nine patients was 57 years and these patients had malignant tumors. In seven patients, the malignancy arose from the epithelial layer, but in two patients sarcomatous changes were identified in the mesenchymal tissues. The older age of the patients with malignant tumors with adequate serial biopsies in two cases supported the thesis that malignant transformation may occur in the benign tumors. Moreover the location of the tumor in one of our patients in whom the resected tumor was associated with anomalous right hepatic ducts and portal veins supported the theory that these tumors develop embryologically from nests of primitive hepatobiliary endodermal and mesodermal cells. Although surgical treatment was performed in all patients, 25% of the patients with benign hepatobiliary cystadenoma with mesenchymal stroma (CMS), and 33% of the patients with malignant CMS had tumor recurrence after primary resection. Ninety per cent of these patients had an incomplete resection at the time of their initial operations. Forty-four per cent of the patients with malignant CMS died after a mean follow-up of 17 months. We conclude that CMS (Edmonson's tumor) occurs uniquely in young female patients, develops from nests of primitive embryonal cells, has the potential for malignant transformation, and should be completely resected at primary operation to avoid recurrence.

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HEPATOBILIARY CYSTADENOMA with mesenchymal stroma (CMS tumor) was first identified by Wheeler and Edmonson as a distinct clinicopathologic entity.[1] These authors called attention to the exclusive occurrence of these tumors in young women, reported their potential to transform into carcinoma, and therefore recommended complete surgical removal of these neoplasms. On microscopic examination this tumor is distinguished by the presence of moderately dense mesenchymal stroma interposed between an inner epithelial lining and an outer connective tissue layer. This stroma is composed of spindle cells similar to the primitive embryonic mesenchymal cells that contribute to the connective tissue surrounding the bile ducts. Moreover the cuboidal-to-low-columnar epithelial cells lining the cyst resemble the endodermal cells from which hepatocytes and biliary epithelium evolve.[2] These histologic findings led Wheeler and Edmonson to hypothesize that these tumors arise from ectopic rests of embryonic bile ducts.[1]

In a review of cystic disease of the liver at the Mayo Clinic between 1907 and 1971,[3-6] the overall incidence of hepatobiliary cystadenoma was 5 among 227 patients (2.2%). In this paper we report three cases of CMS from Duke University Medical Center and review present knowledge of these unusual tumors in 50 additional cases identified in the literature. Interestingly one of our patients had an associated congenitally anomolous right hepatic duct system.

Case Reports (Tables 1 and 2)

Case 1

Patient 1 is a 46-year-old woman who presented to her physician with a right upper quadrant mass and was found by ultrasonography and computed tomographic (CT) scan to have a multiloculated hepatic cyst. Her surgeon partially excised and marsupialized this cyst, which was located in the posteromedial aspect of the gallbladder. Histologic examination revealed a multilocular cystadenoma. The patient remained free of symptoms for 2 months, afterwhich the pain recurred. Repeat ultrasonography and CT scan of the abdomen revealed recurrence of the cyst in the same area (Fig. 1). She was then referred to Duke Medical Center for final treatment.

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TABLE 1. *CMS Tumor: Demographics, Presentation, Radiologic Diagnosis, and Risk of Factors in Three Patients at Duke University Medical Center*

Patient	Sex	Age	Presentation	Radiologic Diagnosis	Risk Factors
1	F	46	Abdominal pain RUQ mass	Ultrasound CT scan	Estrogen replacement
2	F	27	Abdominal pain jaundice, increased liver function tests RUQ mass	Ultrasound Liver spleen scan	Oral contraceptives
3	F	22	Abdominal discomfort Abdominal mass	Ultrasound CT scan	Oral contraceptives

At Duke it was noted by endoscopic retrograde cholangiopancreatography (ERCP) that no true right hepatic duct was present and that the segmental right anterior and posterior hepatic ducts emptied separately into the left hepatic duct (Fig. 2). It was also noted on a late-phase arteriogram that the two right segmental branches of the portal vein arose separately from the left portal vein (Fig. 2).

At operation, examination of the liver revealed a 6-cm mass that occupied the inferior right hepatic lobe. The cystic mass could be palpated in the porta hepatis where its superior medial extension could be seen to bow the segmental right anterior hepatic duct superiorly. The posterior segmental right hepatic duct was posteromedial to the mass, as were the right posterior segment of the portal vein and the right hepatic artery. Because of the large intrahepatic component of the cyst, a partial right hepatectomy was performed using the CUSA (Fig. 1). With careful preservation of the vessels and bile ducts supplying the superior right lobe, the cyst was separated from the porta hepatis anteromedially, from the vena cava posteriorly, and from multiple intrahepatic bile ducts that the tumor was compressing. Histologic examination of the specimen revealed the typical features of a CMS tumor (Fig. 3).

Twelve months after operation the patient was doing well with no recurrence of her tumor.

Case 2

Patient 2 is a 27-year-old woman who, during the investigation of jaundice and right upper quadrant mass at Duke, was found by ultrasonography to have a cystic mass of the liver. Two attempts at canulating the common bile duct by ERCP failed and she was then surgically explored. At operation it was evident that an 8-cm cystic mass, located between the falciform ligament and the gallbladder, was compressing the common hepatic duct. The cyst wall away from the hepatic parenchyma was excised and all remaining loculations were emptied. After operation the jaundice failed to clear and 11 days after her first operation she was returned to the operating room for exploration of her common bile duct. A 4-cm polypoid mass was found in the lumen of the common hepatic duct. This mass was completely resected and a T-tube was left in place. Microscopic examination of the specimens resected at the first and second operations revealed identical histology consistent with CMS. After operation granulation tissue formed in her main hepatic duct. These were surgically resected 3 months after her second operation. A 6-year follow-up of the patient revealed no tumor recurrence.

Case 3

Patient 3 is a 22-year-old woman who, during a period of 5 months noticed a gradual increase in her abdominal girth associated with indigestion and heartburn. A large mass, inseparable from her liver was palpated on physical examination by her physician. An ultrasonographic examination showed a large cystic multiloculated lesion in the upper abdomen that did not appear to arise from the pancreas or kidneys. She was referred to her surgeon who, at exploration, found that the cyst arose from the undersurface of the left lobe of the liver. He emptied 4.2 liters of bile-stained fluid from the cyst and then partially resected it. Final pathologic diagnosis was benign biliary cystadenoma.

The patient did well for the next 3 years. However during a routine examination she was noted to be slightly jaundiced and to have elevated liver function tests. A few months later she began to have right upper quadrant pain and felt that she was gaining weight. At this time she came to Duke University Medical Center for evaluation and treatment. An abdominal CT scan of the abdomen disclosed a 22 × 15 cm cystic mass involving the entire left lobe of the liver, and normal intrahepatic bile ducts. At operation the right hepatic lobe was closely adherent to the tumor and a hepatic trisegmentectomy was performed. The patient's postoperative course was uneventful and she was discharged 2 weeks after her operation. Her last follow-up 9 months after operation, which included a liver–spleen scan, showed no evidence of recurrence. The

TABLE 2. *CMS Tumors: Location, Surgical Treatment, Pathology, and Outcome in Three Patients at Duke University Medical Center*

Patient	Location of Tumor	Initial Therapy (Elsewhere)	Time to Reoperation (Months)	Final Surgery	Histology	Follow-up After Final Surgery (Months)
1	Right hepatic lobe marsupiliation	Partial resection	4	Right hepatic lobectomy	CMS	12
2	Common hepatic duct and right hepatic tube	Partial resection of right hepatic lobe mass	0.5	Excision of mass from common hepatic	CMS	72
3	Right hepatic lobe and medial segment of left lobe	Partial resection, marsupialization	36	Right hepatic trisegmentectomy	CMS with sarcomatous changes	9

CALCUTTA CENTRAL

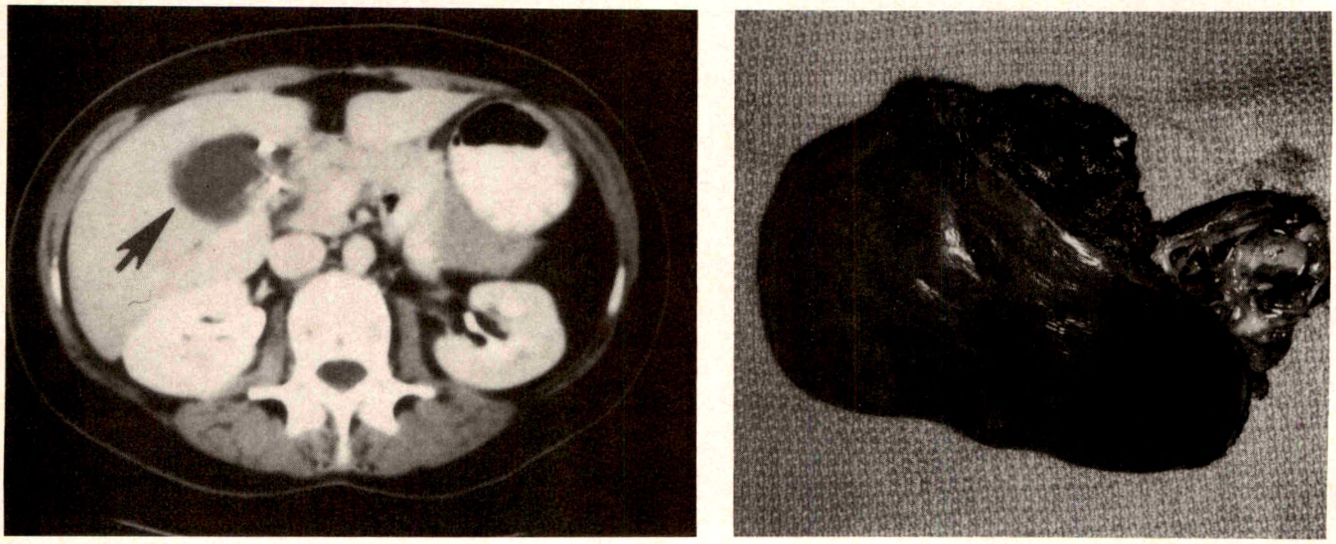


FIG. 1. The left panel is an abdominal CT section at the level of the porta hepatis, demonstrating a 3.5 × 4 cm cystic lesion in the region of the gallbladder fossa, and mildly dilated intrahepatic ducts. The right panel shows the gross specimen consisting of the right lobe of the liver with the tumor extending from the porta hepatis region into the liver parenchyma medially and superiorly.

final pathologic diagnosis was CMS with sarcomatous changes involving the mesenchymal stroma (Fig. 3).

Review of Reported Cases

Demographic

The presence of a distinct mesenchymal stromal layer in the reported cases of benign hepatobiliary cystadenoma could be confirmed in 44 patients, including our reported patients 1 and 2.[1,7–27] All were women with a mean age of 41 years (range, 19–67 years). Malignant transformation was reported in an additional nine women, including our third patient, in whom the presence of mesenchymal stroma in the cyst wall was confirmed.[1,27–32] Their mean age was 57 years (range, 22–75 years).

Presentation (Table 3)

Among the patients with benign cystadenoma, 24 (55%) complained of severe constant dull pain in the region of

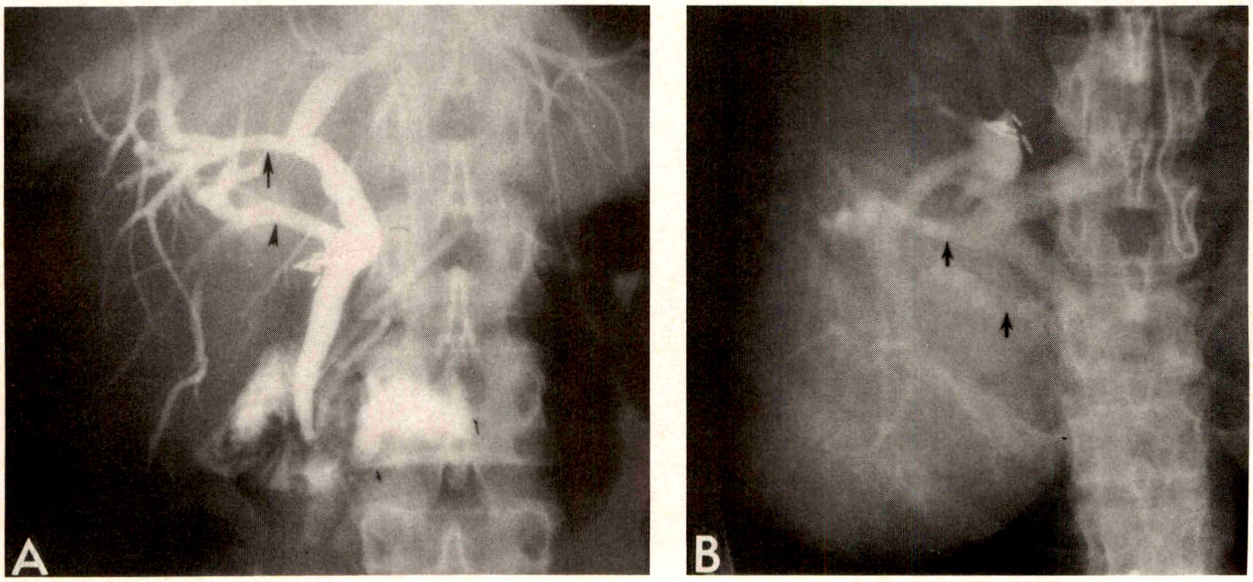


FIG. 2. The left panel is an ERCP on patient 1, showing the biliary tree anomaly characterized by the absence of a true right main hepatic duct with the segmental right anterior hepatic duct emptying superiorly to the segmental right posterior hepatic duct into the left main hepatic duct. The right panel is a late-phase arteriogram on the same patient showing that the two right segmental branches of the portal vein arise separately from the left main portal vein.

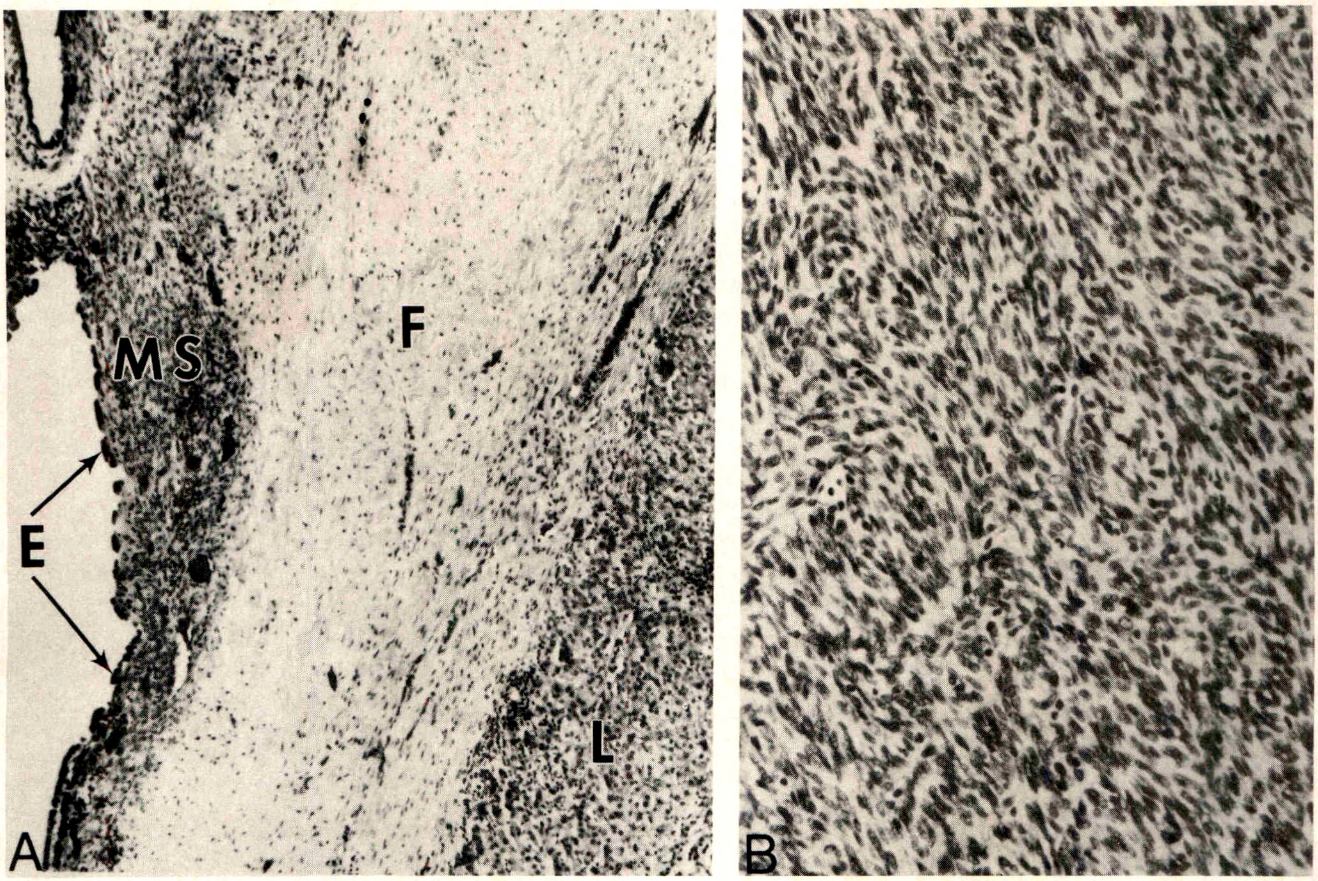


FIG. 3. A typical CMS tumor (patient 1) is shown at left. A cyst is present, lined by cuboidal epithelial cells (E) with a subjacent layer of mesenchymal stroma cells (MS) and a layer of dense fibrous tissue (F). Liver parenchyma (L) is also seen (× 54). At right, malignant transformation of the mesenchymal stroma in patient 3 resulted in this densely cellular sarcoma (× 170).

the right upper quadrant[1,7–13,15,17–19,21,25–27] and seven patients (16%) complained of diffuse abdominal discomfort.[1,16,19,25] Twenty-six patients (59%) complained of an abdominal mass that was freely movable with respiration and confirmed by physical examination in the right upper quadrant or epigastrium.[1,7,8,10,11,13,15–17,19,21,21–23,25–27] Seventeen patients (39%) had a history of intermittent or constant jaundice.[1,8–10,12–14,18–20,22,24,26] Other signs and symptoms reported included elevation of one or more of the liver function tests in 10 patients (23%),[14,18,20–24,26] nausea or vomiting in 7 patients (16%) and ascites in 1 (0.02%) patient.[21] The mean duration of symptoms before final treatment was 2.2 years and varied from 5 days to 17 years in 35 patients in whom it was reported.[1,7,9–17,19–23]

All patients with malignant CMS complained of abdominal swelling, discomfort, or pain at the time of presentation. One of them had elevated liver function tests[27] and in patient 3 those tests were abnormal on one occasion (Table 3). The duration of symptoms in six of these patients in whom it was reported were 5 weeks,[1] 3 months,[1] 5 months (patient 3), 1 year,[30] and 2 years in two patients, respectively.[28,31]

TABLE 3. *Presentation*

Presentation	% of 53 Patients
Pain/Discomfort	75
Abdominal mass	53
Jaundice	32
Elevated liver-function tests	21
Nausea, vomiting	13
Ascites	0.02

Diagnosis (Table 4)

A total of 82 diagnostic radiologic procedures were reported in 30 patients. An abdominal ultrasound done in 12 patients revealed a fluid-filled mass with internal echoes in 11[17,21–26,27] and was unrevealing in one.[20] Eleven patients underwent radionuclide liver scans that demonstrated a cold area in the liver in all cases.[14,16,17,19,21,25,27,30] Upper and lower gastrointestinal series were performed in 12 patients and showed displacement of the duodenum,

P. 24, 803

TABLE 4. *Radiographic Evaluation*

Test	No. of Patients	No. of Positive Findings
Ultrasound	12	11
Upper and lower GI	12	7
Angiography*	11	11
Liver scan	11	11
ERCP & PTC	9	9
Cholecystogram	8	2
CT scan	6	6
IVP	6	2
KUB	5	2
Tomogram	1	1
^{131}T-Rose Bengal	1	1

* Angiography provided information about location and feeding vessels, and showed all tumors to be predominantly hypovascular.

stomach, or colon by a mass in seven cases[15,16,19,21,30] and no abnormalities in five.[11,13,19,27] A cholecystogram performed in 8 patients was normal in 6,[11,17–19,26,30] showed stones in 1,[19] and failed to visualize the gallbladder in 1 patient.[9] Plain film of the abdomen was the first radiologic test in 5 patients, was unrevealing in 3,[21,24,25] and confirmed the presence of a soft-tissue density in the right upper quadrant in 2 patients.[22,23] Six patients[11,16,19,28,30] underwent intravenous pyelogram (IVP), which showed displacement of a kidney or ureter in two patients.[16,19] Eleven patients had an angiography that showed the mass to be mostly avascular in all cases.[15,17,21,23,25,27] Endoscopic retrograde cholangiopancreatography (ERCP) successfully performed in five patients[18,20,22,26] and percutaneous transhepatic cholangiography (PTC) performed in four patients[20,22,24] showed obstruction or compression of the biliary tree in all cases and an anomalous right hepatic biliary tree in our patient. CT scan of the abdomen confirmed the presence of a cystic mass in the liver in all six patients in whom it was done.[23,25,27] An abdominal tomogram performed in one patient[30] revealed a mass in the right upper quadrant of the abdomen. A ^{131}T-Rose Bengal study performed in one patient[19] was compatible with extrahepatic biliary obstruction.

Other diagnostic tests performed included a peritoneoscopy in one patient[26] and a liver biopsy in three patients with jaundice, which revealed cholangitis and pericholangitis.[20,26] An alpha fetoprotein serum level performed in three patients,[17,23] a hydatid complement fixation test or echinococcus skin test in three patients,[21,23,25] and amebic titers in our second patient were all normal. A history of abdominal trauma, weight loss, excessive consumption of alcohol, exposure to animals, and family history of liver or kidney cysts were usually ruled out by history in most patients.

Surgical Therapy (Table 5)

All 53 patients underwent an exploratory laparotomy for final diagnosis and treatment. The mass was confined to the right lobe of the liver in 12 patients[1,7,11,13,19,27,32] and to the left lobe in 13 patients.[1,16,17,21,22,25,27,28,30,31] Both lobes were involved in 12 patients[1,15,19,21,23] and the porta hepatis in another two patients.[1,17] In four patients the tumor originated from one of the hepatic ducts and extended into the liver parenchyma.[14,19,26,27] The right lobe of the liver and the common hepatic duct were separately involved in our second patient. The tumor was present only in one of the major biliary ducts in five patients[10,12,18,20,24] and in the gallbladder in one patient.[8] The origin of the tumor was unknown in three patients.[1,9,29]

At the time of primary operation, 27 patients[1,7,11,12,14,17–20,22–24,27,28,31] underwent total excision of the mass without major hepatic resection. Ten patients required a left partial or total hepatic lobectomy.[1,16,21,25–28,30] Two patients had total left and partial right hepatic lobectomies.[1] Marsupialization or partial excision was performed in nine patients.[1,9,10,21,29] Two patients[13,32] underwent tube drainage and another two had a Roux-Y-limb construction for drainage after partial excision.[1] The patient with tumor confined to the gallbladder had a cholecystectomy[8] (Table 5).

Pathology

The cystadenomas ranged in size from 3 cm to 24 cm at the greatest diameter. They were multilobulated with a smooth surface and fine vasculature. Most tumors were multiloculated and contained fluid that was described as mucinous with various colors. The internal surface was generally smooth with occasional trabeculations described. When malignant, the interior of the cyst showed solid tissue masses protruding from the internal wall. On light microscopy, CMS invariably consisted of three layers: (1) a cyst lining of columnar-to-cuboidal, mucin-secreting epithelium; (2) a moderately to densely cellular stroma composed of spindle (rarely oval) cells; and (3) a dense

TABLE 5. *Surgical Treatment of 53 Patients with CMS*

Primary Operation	No. of Patients	No. of Patients Reoperated for Recurrence
Total excision of tumor	24 (3)	1
Left partial or total lobectomy	9 (1)	0
Partial right and left lobectomies	2	0
Partial excision or marsupialization	5 (4)	4, 1*, (1, 1*)
Tube drainage	1 (1)	1 (1*)
Roux-Y-limb drainage	2	0
Cholecystectomy	1	0
Total	44 (9)	6, 1*, (1, 2*)

Numbers in parentheses represent patients with malignant CMS.
* Patients requiring more than one operation for recurrence.

layer of collagenous connective tissue (Fig. 3). Portal areas adjacent to the tumor appeared to be hamartomatous in two patients[1,27] and two others, including our first patient, who showed periportal cholangiolar proliferation.[1] Malignant change, when it occurred, took place in the epithelial component as papillary adenocarcinoma in seven cases[1,27,28,30–32] and in the mesenchymal stroma as sarcomatous changes in patient 3 (Fig. 3) and of equivocal origin in one patient.[29] Although the malignant change was reported as occurring in the mesenchymal stroma in this last case,[29] an epithelial origin with invasion into the stroma could not be ruled out on reviewing the pictures and comparing them to the histologic findings in patient 3.

Ultrastructural examination of this tumor on a glutaraldehyde-preserved specimen are reported here for the first time. Samples were taken from the mesenchymal solid portion of the tumor in patient 3, were fixed in glutaraldehyde, and processed for electron microscopy. Ultrastructural examination revealed primitive spindled-shaped cells within a collagenous matrix. The cells generally had much less rough endoplasmic reticulum than typical fibroblasts. Also, unlike fibroblasts, the cells often exhibited a stellate profile when cut transversely. In a few cells minimal smooth-muscle differentiation was present as evidenced by peripheral, longitudinally oriented filaments with fusiform densities, and by frequent intermediate junctions, very reminiscent of the findings of myofibroblastic cells (Fig. 4).

Outcome of Therapy

Twenty-one of the patients with benign CMS did very well for a mean follow-up period of 6 years (range, 0.5–18 years).[1,12,14,18,19,23,24,27] Reoperation for recurrence of benign CMS was necessary in seven patients. In one of these patients, the tumor was reported to be completely resected at the time of primary operation.[1] A second pa-

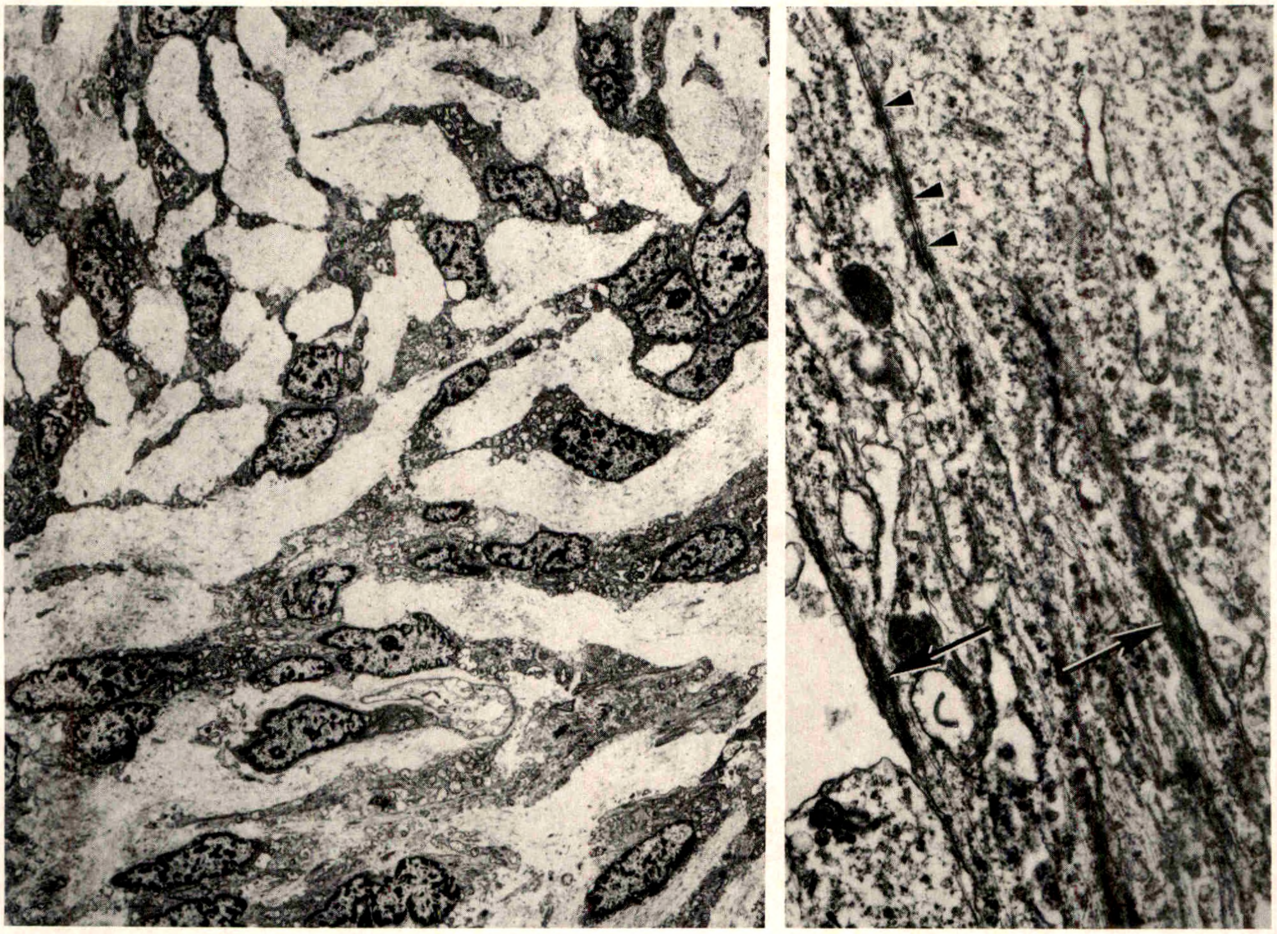


FIG. 4. The electron photomicrograph from tumor in patient 3 at left demonstrates the spindle-to-stellate profiles of malignant mesenchymal stromal cells in a CMS tumor (× 1600). Higher magnification at right illustrates frequent junctions (arrowheads) and small numbers of peripheral longitudinally oriented filaments with poorly formed fusiform densities (arrows). These features were present in a few malignant mesenchymal stromal cells and indicate slight smooth-muscle differentiation, similar to that observed in myofibroblasts (× 21,000).

tient had only tube drainage[13] and four others, including our first and second patients, had partial excision of the tumor at the time of primary operation.[1,10] The tumor excised during the second operation in patient 2 was independent from the tumor excised during the first operation. The last patient had reoperation twice for recurrence after partial excision at the first two operations[19] (Table 5). No follow-up information is available on the other 16 patients with benign CMS.

Four of the patients with malignant CMS died secondary to liver involvement by tumor or distant metastases at 10 days,[29] 1 month,[1] 6 months,[28] and 5 years[1] after the diagnosis of malignant transformation. Only one of these patients had total excision at primary operation.[28] Two others had partial excision of their tumors and one had a partial excision after a marsupialization the first time. Three other patients are alive at 5 years[30] after a left lobectomy and at 6 months[27] and 38 months[31] after total excision. Patient 3, who underwent a trisegmentectomy 3 years after a partial resection, was doing well on her last follow-up, 9 months after her second operation. The last patient with malignant CMS required drainage three times before partial excision at the fourth operation.[32] She was doing well 8 months after her fourth operation (Table 5).

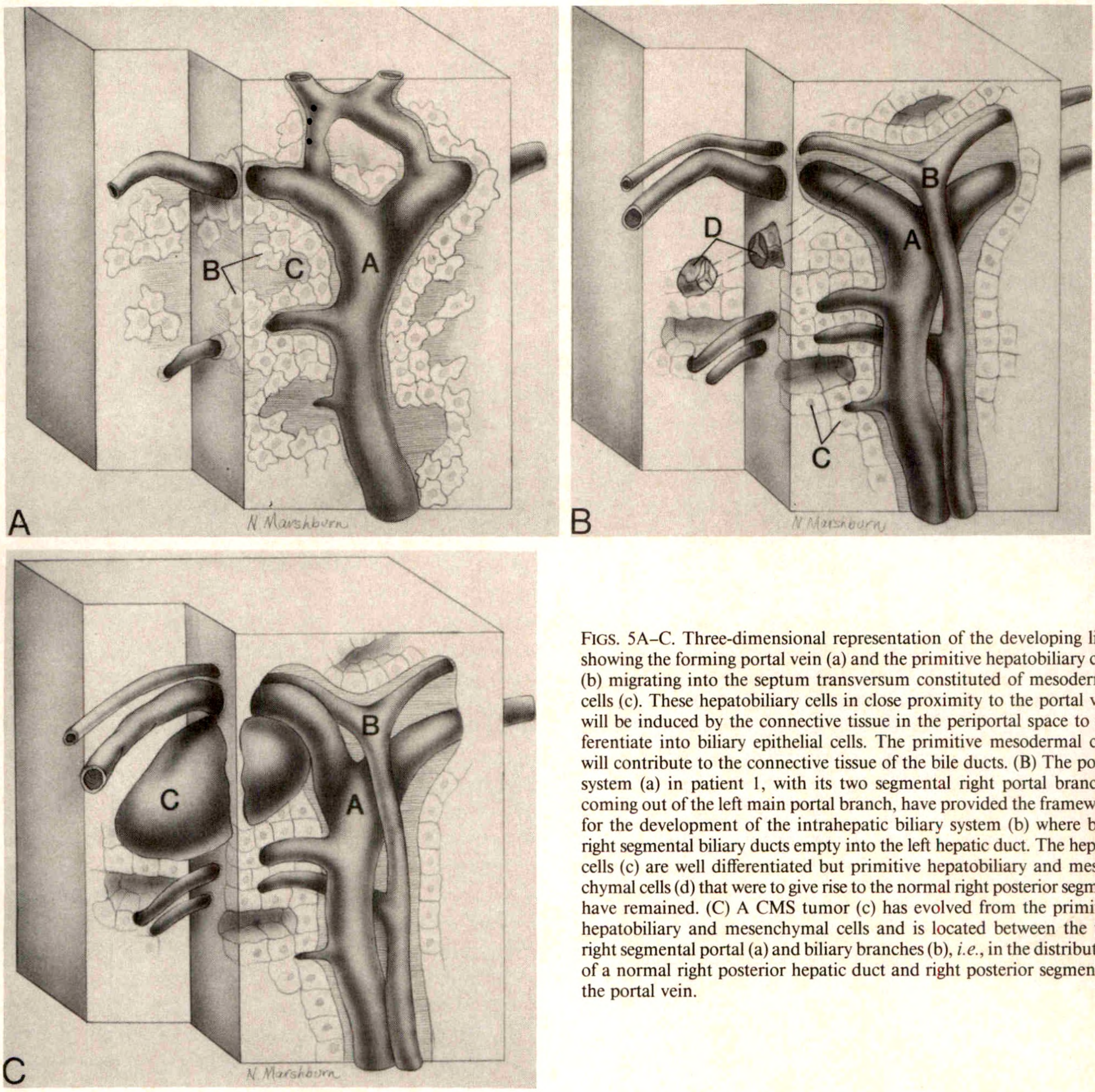
Discussion

Patients with CMS tumors present in a manner similar to patients with other liver masses. The most common symptoms are pain and abdominal discomfort, and one can often palpate a mass in the right upper quadrant (Table 1). When the tumor involves or compresses one of the major biliary ducts, jaundice and elevation of liver function tests occur. Compression of the vena cava or hepatic veins by a large mass may lead to ascites, as seen in one case. On the other hand, compression of any part of the gastrointestinal tract can cause obstruction, nausea, and vomiting.

Although the right upper quadrant pain, mass, jaundice, and elevated liver function tests might point to a hepatobiliary abnormality, the suspicion for a cyst is usually low. Upper and lower gastrointestinal series done to rule out primary gastrointestinal lesions and IVP done to rule out kidney stones or tumors were nonspecific in most cases (Table 2). Cholecystograms, liver scans, PTC, and ERCP confirmed the presence of a hepatic mass. Angiography showing that the mass was avascular, coupled with a negative alpha fetoprotein, ruled out the possibility of hepatoma in patients with a long history of estrogen-replacement therapy. Ultrasonographic examination of the right upper quadrant provided the best clue as to the hepatobiliary origin and cystic nature of the mass (Table 2). When history of exposure to animals was ruled out, an aspiration of the cyst helped to relieve some of the symptoms but could not diagnose the nature of this cyst, except for excluding its parasitic, traumatic, or inflammatory origin.[33] Surgical approach was definitive in providing the final diagnosis in all cases. CT scan of the abdomen that provided information about the exact location of the cystic mass and selective angiographic studies that showed the blood vessel distribution helped to guide the surgeon during resection (Figs. 1 and 2). The ERCP performed in our patient detected the anomalous biliary tree and thus helped us to avoid a major catastrophe during surgery (Fig. 2). The final primary pathologic diagnosis in most cases was reported as hepatobiliary cystadenoma. It was not until 1985 that Wheeler and Edmonson,[1] on reviewing most of these cases, reclassified them as cystadenoma with mesenchymal stroma.

Cystadenoma with mesenchymal stroma is classically described as multiloculated on gross examination with three distinct tissue layers on microscopy (Fig. 3): an inner layer of mucin-producing columnar-to- cuboidal cells; an intermediate layer of undifferentiated mesenchymal cells; and an outer layer of collagenous connective tissue. Histologically it is differentiated from the hepatobiliary cystadenoma by the presence of the intermediate layer of mesenchymal cells. Embryologically and clinically these two tumors also appear to be different.

Embryologically the primitive cells that later differentiate into hepatic or biliary epithelial cells are of endodermal origin.[34] These endodermal cells, called primitive hepatobiliary cells, arise from the cephalic part of the hepatic diverticulum, which itself is an outgrowth of the distal foregut. These cells migrate into the adjacent septum transversum (Fig. 5A), a structure of mesodermal origin that contributes to the connective tissue of the bile ducts, blood vessels, as well as the endothelial cells of the liver sinusoids.[34] At about the 8-mm stage of embryonal life, the primitive hepatobiliary cells differentiate into the epithelial cells of the intrahepatic bile ducts. This differentiation is partly induced by the presence in the portal spaces of forming connective tissue (mesoderm).[35] However intrahepatic bile ducts will not form until these hepatobiliary cells come in contact with a previously formed duct. This happens at the hilum where they come in contact with the main hepatic duct,[2] which together with the cystic duct and gallbladder originate from the caudal part of the hepatic diverticulum. The growth of these intrahepatic bile ducts thus proceeds from the hilum toward the periphery along the framework provided by the portal vein and its branches[35] (Fig. 5B). The first patient presented here is a clear example of this developmental anatomy. To our knowledge this is the first report of an anomalous portal tract that is paralleled by a similarly anomalous biliary tree. In this patient the two right segmental branches of the portal vein arose directly from the left main branch (Fig. 2). Moreover, and as demonstrated by ERCP, both right segmental biliary ducts emptied into the main left hepatic duct (Fig. 2). The posterior right



FIGS. 5A–C. Three-dimensional representation of the developing liver showing the forming portal vein (a) and the primitive hepatobiliary cells (b) migrating into the septum transversum constituted of mesodermal cells (c). These hepatobiliary cells in close proximity to the portal vein will be induced by the connective tissue in the periportal space to differentiate into biliary epithelial cells. The primitive mesodermal cells will contribute to the connective tissue of the bile ducts. (B) The portal system (a) in patient 1, with its two segmental right portal branches coming out of the left main portal branch, have provided the framework for the development of the intrahepatic biliary system (b) where both right segmental biliary ducts empty into the left hepatic duct. The hepatic cells (c) are well differentiated but primitive hepatobiliary and mesenchymal cells (d) that were to give rise to the normal right posterior segment have remained. (C) A CMS tumor (c) has evolved from the primitive hepatobiliary and mesenchymal cells and is located between the two right segmental portal (a) and biliary branches (b), *i.e.*, in the distribution of a normal right posterior hepatic duct and right posterior segment of the portal vein.

portal or biliary segment failed to join the anterior right portal or biliary segment to form the right main portal vein or hepatic duct. The tumor in this case is located between the two right segmental portal and biliary branches, *i.e.*, in the distribution of a normal right posterior hepatic duct and right posterior segment of the portal vein (Fig. 5C). It is possible that the hepatobiliary cells that were to give rise to the normal right posterior segment, along with their associated mesenchyme, evolved into the neoplasm in this patient (Fig. 5B). This hypothesis is further strengthened by the histologic similarity of the cuboidal-to-columnar epithelial cells to the primitive hepatobiliary cells, and the similarity of the mesenchymal stroma to primitive mesoderm. In contrast hepatobiliary cystadenoma without mesenchymal stroma was shown in experimental models to arise from ductal epithelium in response to various stimuli such as carcinogens[29] or ischemia.[36] They might develop from the ductal epithelial cells of either small proliferating cholangiolar ducts[37] or as outgrowths of the normal bile ducts.[38] It is interesting to note that small cholangiolar proliferations have been associated with both CMS[1] and cystadenomas without mesenchymal stroma.[39] To link the normal embryologic events with the above observations, it becomes clear that a foci of primitive hepatobiliary and mesenchymal cells is necessary to start the events (Fig. 6). These primitive cells could be present in the liver parenchyma, in close proximity or in the wall of a bile duct, or in both locations simultaneously as represented by patient 2. Under normal maturation conditions, these will give rise to the normal intrahepatic ducts (Fig. 6). If these conditions are suboptimal, as seen with ischemia, they will give rise to small cholangiolar ducts.[37] In young women, and under a mysterious stimulus, these cells will differentiate into a CMS tumor. Estrogen, which was taken for a long time by both patients 1 and 2 and reported in another patient,[22] could be the stimulus for the growth of this tumor from the primitive cells. If both this stimulus and suboptimal conditions exist, both a CMS tumor and cholangiolar ducts will coexist. In the presence of ischemia, carcinogens, or other stimuli, a cystadenoma without mesenchymal stroma will arise from either the normal intrahepatic ducts or from cholangiolar ducts if these already exist. These same stimulating factors might be those that give rise to anomalies observed in other organs like the kidneys[19] and pancreas[40] because these have only been observed in cystadenomas without mesenchymal stroma. On the other hand, the hamartomatous changes that have been observed in both tumors[1,19,27] are an indication of the similar origin of both tumors from the pluripotential primitive hepatobiliary and mesenchymal cells (Fig. 6).

Clinically we have seen that CMS is exclusive to young women. Cystadenoma without mesenchymal stroma was shown to occur in both men and women at a peak incidence age of 50 years.[1] Moreover it was shown that cystadenocarcinoma with mesenchymal stroma has been shown to arise from CMS, a relationship not well established for the cystadenoma and cystadenocarcinoma without mesenchymal stroma. In one case[32] followed by serial biopsies, the epithelial component of CMS underwent papillary proliferation and stromal invasion. It is noteworthy that the mesenchymal cells can also be the source of malignant growth in the form of sarcomatous changes as seen in patient 3.[29] In this patient the sarcomatous changes were seen in the second but not the first specimen. Although the malignant part could have been missed in the first surgical specimen, it could also represent a malignant transformation during a 3-year period. This malignant change over time, whether in the epithelial or mesenchymal component, is validated by the older age and larger masses of the nine patients identified as having cystadenocarcinoma with mesenchymal stroma.[1,29–32] Although no evidence at the present time exists concerning the potential malignant change of cystadenoma without mesenchymal stroma, the 14 cases of cystadenocarcinoma without mesenchymal stroma are speculated to be malignant neoplastic outgrowths of biliary or cholangiolar ducts.[18] In a recent case report, foci of atypical as well as frankly malignant epithelial cells with some invasion of the cyst wall were shown to be present in an otherwise benign biliary cystadenoma without mesenchymal stroma. In this case the authors emphasized careful pathologic evaluation after thorough sectioning.[41]

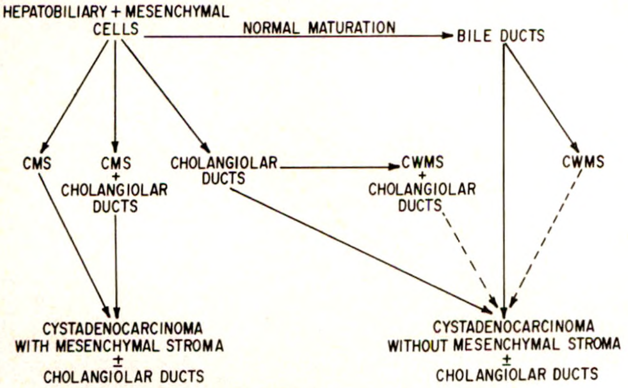

HEPATOBILIARY + MESENCHYMAL CELLS
NORMAL MATURATION
BILE DUCTS
CMS
CMS + CHOLANGIOLAR DUCTS
CHOLANGIOLAR DUCTS
CWMS + CHOLANGIOLAR DUCTS
CWMS
CYSTADENOCARCINOMA WITH MESENCHYMAL STROMA ± CHOLANGIOLAR DUCTS
CYSTADENOCARCINOMA WITHOUT MESENCHYMAL STROMA ± CHOLANGIOLAR DUCTS

FIG. 6. The development of CMS necessitates a foci of primitive hepatobiliary and mesenchymal cells, which under normal maturation conditions give rise to the biliary duct system. Under suboptimal conditions, such as ischemia, these cells will develop into abnormal cholangiolar ducts. In young women, and under an unknown stimulus, these cells will become a CMS tumor that can also transform into a cystadenocarcinoma with mesenchymal stroma. If both this stimulus and ischemia are present, CMS will coexist with cholangiolar ducts. Cystadenoma without mesenchymal stroma (CWMS), as well as cystadenocarcinoma without mesenchymal stroma, are neoplastic outgrowths of normal bile ducts or cholangiolar ducts subjected to carcinogens or ischemia. The transformation of CWMS into cystadenocarinoma without mesenchymal stroma is, however, uncertain.

The most successful form of therapy for hepatobiliary cystadenoma with or without mesenchymal stroma is total excision. Although surgical treatment was performed in all patients, 25% of the patients with benign CMS and 33% of the patients with malignant CMS had recurrence of their tumors after primary resection. Ninety per cent of these patients had an incomplete resection at the time of primary operation. Partial excision and drainage, as initially performed in our patients, ensure recurrence. When total excision with lobectomy, if necessary, were performed for benign CMS, no recurrences were noted except in one patient who had a total excision of the tumor. The best outcome for patients with malignant CMS was obtained when a radical operation was performed before metastasis. Survival in patients with malignant CMS was 56% after a mean follow-up of 17 months.

Because pathologists are usually reluctant to diagnose cystadenoma on frozen section,[42] an aggressive approach should be used whenever a neoplastic cyst is suspected, with total excision being the primary goal. A margin of normal liver tissue should be ensured or, in some cases, a lobectomy is recommended because of the occasional malignant transformation. Partial excision and marsupialization should only be reserved for those cases in which total resection is anatomically impossible. Removal of the epithelial lining of the cyst should be as complete as possible in these cases, and follow-up should be thorough because malignant transformation can still occur in the mesenchymal component.

We found the information provided by ERCP very useful in resecting the tumor in our first case. Because aberrant bile ducts can be present with these tumors, the surgeon should be aware of the variant anatomy before undertaking a major resection. Moreover because hepatic CMS may coexist with a similar tumor in the biliary duct system (patient 2), a preoperative visualization of the bile ducts becomes necessary. This will help to differentiate an intrahepatic tumor from simple compression of the bile ducts by the extrabiliary tumor.

We have reported three cases of hepatobiliary cystadenoma with mesenchymal stroma according to the new classification of Wheeler and Edmonson and reviewed the previously reported cases. Clinically these tumors occur exclusively in young women, have the same presentation as other hepatobiliary masses, and are best diagnosed by ultrasonography. Histologically they are differentiated from other cystadenomas by the presence of a primitive mesenchymal stroma. Embryologically these tumors might arise from foci of primitive hepatobiliary and mesenchymal cells as illustrated by our patients who had an aberrant right portal and biliary anatomy. This is in contrast to cystadenomas without mesenchymal stroma that might arise from formed biliary ducts. The malignant potential of these tumors is stressed and complete surgical removal to prevent recurrence is emphasized.

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Postoperative Recurrence of Hepatocellular Carcinoma

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Sixty-nine patients with hepatocellular carcinoma underwent curative hepatic resections as primary cases from 1981 to 1986. Seven patients died in the hospital after operation. The other 62 patients left the hospital and were closely followed for 25 to 78 months. Recurrence of carcinoma became obvious in 41 (66%) of 62 patients. The clinical and pathologic features of these 41 patients were not significantly different from those of the other patients. Recurrent tumors were found in the residual liver in 38 patients (93%), in the bone in 2 (5%), and in the lung in 1 (2%). Recurrence was diagnosed within 1 year, between 1 and 2 years, and more than 2 years after the operation in 22 (56%), 10 (26%), and 7 (18%) patients, respectively. It was difficult to determine the exact time of recurrence in two patients. There was a significant negative correlation between the size of primary tumor and time until recurrence; the larger the primary tumor, the shorter the time until recurrence. Among the 29 patients who underwent local excisions for their primary tumors, 19 recurrences were observed. Eighteen were found in the residual liver, in the same segment as the primary tumor, or in one near it. Larger hepatic resection for primary tumors is thus advocated to prevent recurrence.

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HEPATOCELLULAR CARCINOMA (HCC), a highly malignant disease that carries a poor prognosis, is very common in Asian countries. The incidence of resection for HCC has increased greatly during the last decade because of the progress in diagnostic imaging tools.[1-3] Early detection of HCC has recently become possible and the number of hepatic resections, especially for small HCC, has increased. As a result short-term outcome has improved greatly, as have surgical techniques, and operative mortality rates have been reduced to a few per cent.[4,5] The long-term results, however, are not yet satisfactory. We reviewed our previous hepatic resections for HCC, and found that postoperative recurrence was the main cause of the poor long-term results.[6] In the current study we investigated the postoperative recurrence of HCC to determine how to decrease the incidence of recurrence and improve the long-term results of hepatic resections for HCC.

Patients and Methods

Seventy-three hepatic resections for HCC were performed from January 1981 to December 1986 at the First Surgical Department, Tokyo University Hospital. Three were resections for recurrent tumors in the residual liver, and one was a noncurative resection for diffuse HCC. The other 69 patients underwent curative resections, *i.e.*, macroscopically complete removal of tumor tissue, as primary cases. Clinical records of these 69 patients were reviewed to clarify the details of recurrence. Patients who were discharged from the hospital had been closely followed at our outpatient clinic or affiliated institutions. Blood chemistry, measurement of alpha-fetoprotein (AFP) level, and ultrasonography were performed at least once a month for the early detection of recurrence. Computed tomography was also performed more than twice a year. When recurrence was suspected, angiography and needle biopsy under ultrasonic guidance were performed for confirmation. The follow-up period of the surviving patients ranged from 25 to 78 months (mean, 44.4 months).

Student's t test, chi square test, Fisher's exact method, and simple regression analysis by the least squares method were used for statistical analysis. Survival curves of patients experiencing recurrence were obtained using the Kaplan-Meier method,[7] and survival curves were compared by the generalized Wilcoxon test.[8] A value of $p < 0.05$ was considered significant.

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Results

Profile of Operated Patients with HCC

The mean age at operation of the 69 patients was 57.4 years, and their ages ranged from 26 to 77 years. Fifty-nine patients (86%) were men and 10 (14%) were women. Liver cirrhosis was present in 52 patients (76%), and other chronic liver diseases, such as chronic hepatitis and liver fibrosis, were found in 14 patients (20%). HCC was diagnosed in an otherwise normal liver in only three patients (4%). Hepatitis B surface antigen was measured by reversed passive hemagglutination test in 67 patients and was positive in 14 (21%). The preoperative serum level of AFP was measured by radioimmunoassay in 67 patients. While the normal value is lower than 20 ng/mL, it was higher than 20, 200, and 2000 ng/mL in 50 (75%), 23 (34%), and 11 (16%) patients, respectively.

Table 1 presents the details of the operations performed on the 69 patients. Major hepatic rejections, *i.e.*, bisegmentectomies (lobectomies), were carried out on 25 patients (36%). Minor hepatic resections, *i.e.*, segmentectomies and local excisions, were performed on 44 patients (64%).

The tumor was solitary in 58 patients (84%), and multiple in 11 (16%). Two tumor nodules were found in six patients, three in four patients, and more than three in one patient. Investigation of the resected specimens revealed that 79% of the main tumors were encapsulated by fibrous tissue. The maximal diameter of the main tumor varied from 0.5 cm to 16.3 cm. It was less than 2 cm in 12 (17%) patients, between 2 cm and 5 cm in 37 (54%), between 5 cm and 10 cm in 11 (16%), and more than 10 cm in 9 (13%) patients.

Figure 1 shows the outcomes in the 69 patients. Seven patients died in the hospital after the operation, yielding a hospital mortality rate of 10%. Six patients died of liver failure and one patient died of postoperative intra-abdominal bleeding. The other 62 patients were discharged from the hospital. Thirty-five of the 62 patients have died. Recurrence of HCC was the cause of death in 26 patients. Five patients died of hepatic failure due to severe cirrhosis. Rupture of esophageal varices was the cause of death in one patient. The other three patients died of diseases not related to the liver. Although 27 of the 62 patients were still alive at the time of this inquiry (January 1989), recurrence of HCC had become obvious in 15. The other 12 patients were living without any signs or symptoms of recurrence.

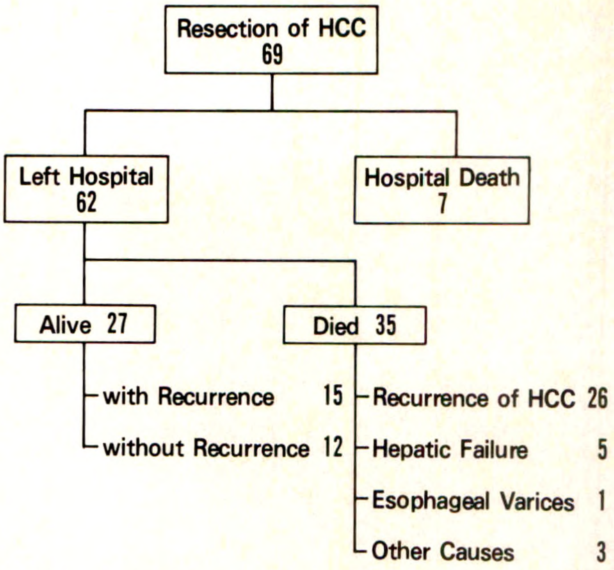


FIG. 1. Results in 69 patients with HCC who underwent operation between 1981 and 1986 (final compilation, January 1, 1989).

TABLE 1. *Operations Performed on 69 Patients with HCC*

Operation	HCC with LC	HCC Without LC	Total
Right lobectomy	8	11	19
Left lobectomy	3	2	5
Central bisegmentectomy	1	0	1
Segmentectomy	14	1	15
Local excision	26	3	29
Total	52	17	69

HCC, hepatocellular carcinoma.
LC, liver cirrhosis.

Patients with Recurrence

Postoperative recurrence of HCC was observed in 41 (66%) of 62 patients during the follow-up period. Table 2 shows the details of these 41 patients with recurrence in comparison to the other 21 patients. The seven patients who died in the hospital after operation were excluded from this inquiry. There was no significant difference between these two groups of patients for any item in the table. That is the clinical and pathologic features of patients with recurrence were no different from those of the other patients. This indicates that patients with recurrence are in no way special; any patient is subject to the recurrence of HCC after hepatectomy.

Sites and Times of Recurrence

The first recurrent tumor was found in the residual liver in 38 patients (93%), in the bone in 2 (5%), and in the lung in 1 (2%). The recurrent tumor became obvious within 1 year, between 1 and 2 years, and more than 2 years after the operation in 22 (56%), 10 (26%), and 7 patients (18%), respectively. It was difficult to determine the exact time of recurrence in two patients. These results indicate that recurrence occurs most often in the residual liver and within a very short time after operation.

TABLE 2. *Clinical and Pathologic Characteristics of 41 Patients With Recurrence in Comparison with 21 Patients Without Recurrence*

Characteristic	Recurrence (+) (No. of Patients)	Recurrence (−) (No. of Patients)	Total
Number of patients	41	21	62
Mean age (years)	57.8	56.4	57.3
HB surface antigen			
Positive	8	4	12
Negative	31	17	48
Alpha-fetoprotein			
≦200 ng/mL	27	13	40
>200 ng/mL	12	8	20
Liver cirrhosis			
Yes	29	16	45
No	12	5	17
Number of tumors			
Solitary	34	18	52
Multiple	7	3	10
Tumor size*			
≦5 cm	29	13	42
>5 cm	12	8	20
Fibrous capsule			
Yes	31	18	49
No	9	3	12
Operation			
Major resection†	14	8	22
Minor resection‡	27	13	40

* Maximum diameter of the main tumor in each patient.
† Bisegmentectomies (lobectomies).
‡ Segmentectomies and local excisions.

Figure 2 shows the relation between the maximal diameter of the primary tumor and the time of recurrence. There was a significant negative correlation between these two indices. The larger the primary tumor, the shorter the time until recurrence.

As shown in Table 1, the incidence of minor hepatic resections for HCC has been very high recently. Advances in diagnostic techniques have enhanced the early detection of small HCC through the follow-up of patients with chronic liver diseases. Local excision, smaller than one segment of the liver, is the operation of choice in most instances for such patients because the poor functional reserve of the cirrhotic liver does not permit larger resection. Nineteen recurrences were observed after 29 local excisions. Eighteen (95%) of 19 recurrences were in the residual liver. Recurrent tumor in the liver was solitary in the early stage of recurrence in 17 patients but was multiple from the beginning of recurrence in one. Figure 3 shows the relation between the sites (segments) of primary tumors and recurrent tumors in these 17 patients. Ten recurrences occurred in the same segment as the primary tumor, and seven recurrences were seen in a neighboring segment. No recurrence was observed in a segment of the liver distant from the primary tumor. In the case of major hepatic resection, most recurrent tumors were diagnosed in the segment next to the surgical margin, not in a distant segment. Curative resection of the primary tumor, *i.e.*, macroscopically complete removal of tumor tissue, was performed in every patient in this study. The recurrences that we encountered could be clinically discerned from those arising from remnant cancer tissue at the surgical margin because a cancer-free zone could be identified between the recurrent tumor and surgical margin by ultrasonography or computed tomography.

Risk Factors for Recurrence

Table 3 compares the background factors between two groups of patients: a high-risk group in whom the recurrence became obvious within 1 year after operation, and a low-risk group who survived more than 1 year without recurrence. Patients in whom the recurrence occurred after 1 year of observation were included in the second group. Those who died within 1 year after operation without recurrence were excluded from this investigation. The incidence of tumors measuring more than 5 cm in diameter was greater in the high-risk group than in the low-risk group ($p < 0.05$). However there were no other significant differences between these two groups of patients. Tumor size was the only factor that carried a high risk of early recurrence.

Treatment of Recurrent Tumors

The therapy for recurrent HCC is usually more difficult than that for primary HCC because of the more severe circumstances. In some patients a combination of several therapies was used. Table 4 shows the main therapies performed in each patient. Surgical resection was the treat-

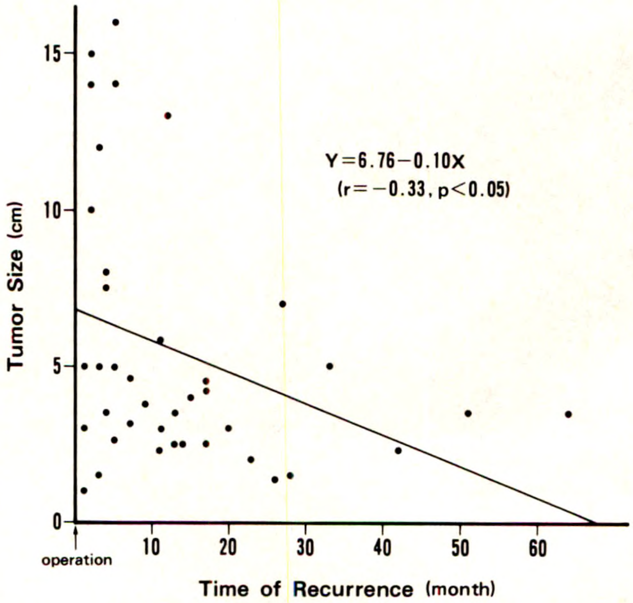
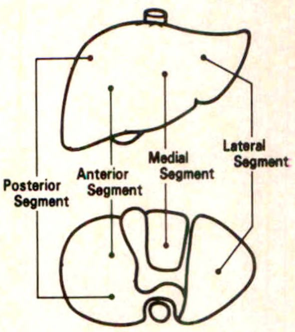


FIG. 2. Relationship between size of primary tumor and time of recurrence.

FIG. 3. Relationship between the segment of primary tumor and that of recurrent tumor in 17 patients who underwent local excision for their primary tumors.

Primary \ Recurrence	Posterior Segment	Anterior Segment	Medial Segment	Lateral Segment
Posterior Segment	0	2	0	0
Anterior Segment	4	10	0	0
Medial Segment	0	1	0	0
Lateral Segment	0	0	0	0



ment of choice for recurrent tumors as well as for primary ones; however it was possible in only 8 (20%) of 41 recurrences. Resection was impossible in the other 33 patients because of the anatomic location of the recurrent tumor and/or poor functional reserve due to cirrhosis. Transcatheter arterial embolization (TAE), the second choice, was performed in 17 patients. Large-dose administration of reduced glutathione (GSH) was used for recurrent HCC in five patients. Our trial, which was based on the report by Novi[9] on her animal experiments, was the first clinical experience with GSH therapy for liver malignancy. GSH at a dose of 5 g/day was administered orally. General chemotherapy was performed in two patients and irradiation was done in one. No therapy for recurrent tumors could be performed in the other eight patients because of their poor general condition.

TABLE 3. *Comparison of Background Factors Between the High- and Low-Risk Groups of Recurrence*

Factor	High-Risk Group* (No. of Patients)	Low-Risk Group† (No. of Patients)	p
Number of patients	22	31	
Mean age (years)	56.9	57.2	NS
HB surface antigen			
Positive	6	5	
Negative	15	25	NS
Alpha-fetoprotein			
≦200 ng/mL	14	21	
>200 ng/mL	7	9	NS
Liver cirrhosis			
Yes	15	23	
No	7	8	NS
Number of tumors			
Solitary	19	28	
Multiple	3	3	NS
Tumor size‡			
≦5 cm	13	26	
>5 cm	12	8	<0.05
Fibrous capsule			
Yes	16	25	
No	5	6	NS
Operation			
Major resection§	10	8	
Minor resection‖	12	23	NS

* Patients in whom the recurrence became obvious within 1 year after operation.

† Patients whose cancer-free period after operation was no less than 1 year.

‡ Maximal diameter of the main tumor in each patient.

§ Bisegmentectomies (lobectomies).

‖ Segmentectomies and local excisions.

Results of Patients with Recurrence

Figure 4 illustrates the survival curve of 39 patients with recurrence as calculated from the time of recurrence. Two patients in whom the exact times of recurrence were uncertain were excluded. Survival rates of 1, 2, and 3 years were 71,% 42%, and 25%, respectively. Differences in survival pattern according to treatment are shown in Figure 5. The best survival rate was obtained after surgical resection, but the difference was not significant.

Discussion

The number of hepatic resections for HCC has increased greatly in most surgical institutions because of recent advances in diagnostic imaging techniques.[1-3] The incidence of small HCC, especially, has increased as a result of its early detection. Minor hepatic resection has been preferred for small HCC because the hepatic functional reserve is too poor to tolerate major hepatic resection. Most HCC is associated with severe liver cirrhosis, and cirrhosis interferes with major resection of liver tissue. Seventy-six per cent of the patients in this series had cir-

TABLE 4. *Main Therapy in Patients with Recurrent HCC*

Therapy	No. of Patients
Resection	8
TAE	17
GSH therapy*	5
Chemotherapy	1
Radiation	1
None	9
Total	41

HCC, hepatocellular carcinoma.

TAE, transcatheter arterial embolization.

* Large-dose administration of reduced glutathione.

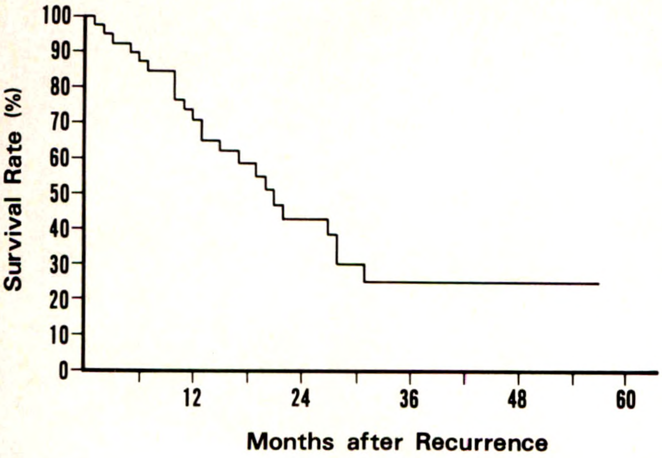


FIG. 4. Survival curve of 39 patients with recurrence (calculated from the time of recurrence).

rhosis, and 20% had other chronic liver diseases. Minor hepatic resection was performed on 77% of the cirrhotic patients, with only 23% undergoing major hepatic resection (Table 1). The short-term operative results have recently improved as a result of limited resection of the liver.[5] The incidence of massive operative bleeding and postoperative hepatic failure has been greatly reduced. However the long-term outcome of patients who survive the postoperative course and are discharged is not yet satisfactory.[6]

Postoperative recurrence of HCC was the major cause of death in patients who were discharged from the hospital and was the main obstacle to the patients' long-term survival. The incidence of postoperative recurrence was extremely high after hepatic resection (Fig. 1). We were unable to find any special characteristics in patients with recurrence (Table 2). That is, postoperative recurrence is not a special phenomenon that occurs in certain patients with HCC.

Subclinical metastases that have happened before operation and/or metachronous multicentric carcinogenesis may play an important role in recurrence. Our study clearly demonstrated that most recurrences occurred near the primary lesion soon after operation (Fig. 3). It also indicated that the size of the primary tumor was directly related to the length of time before recurrence, *i.e.*, the larger the primary tumor, the sooner the recurrence (Fig. 2). These results strongly suggest the importance of metastases. Although HCC can metastasize through the portal vein, hepatic vein, or lymph flow, intrahepatic metastases *via* the portal system have been regarded as the most common mode of metastases[10] and may greatly contribute to recurrence after hepatic resection.

The principles of therapy for recurrent HCC are the same as those for primary HCC. Although the survival curves after several modes of therapy did not show any significant differences, resection is the first choice of treatment whenever it is feasible. However the patient's condition at the time of recurrence is usually worse than at the first operation. The functional reserve of the cirrhotic liver is reduced from the first hepatic resection. Regeneration after hepatectomy does not progress smoothly in the cirrhotic liver.[11] The second operation is technically more difficult than the first one because of adhesions around the residual liver and anatomic changes. TAE is the procedure of choice for unresectable recurrent HCC. However because the recurrent tumor is usually very small at the time of diagnosis due to the close follow-up with ultrasonography and AFP measurement, TAE may damage the nontumorous liver tissue. This therapy cannot be performed on severely cirrhotic patients without the risk of hepatic failure. GSH therapy is indicated for such severely ill patients because it has no side effects other than mild diarrhea in a few patient and does not disturb the quality of life. Its antitumor effect is uncertain in the clinical field, but we are trying it to prolong the survival time for patients with HCC.

The incidence of postoperative recurrence is extremely high and can manifest in any patient with HCC, even those with HCC of less than 2 cm in diameter (Fig. 2). As mentioned above the treatment for recurrent HCC includes several difficult problems. Once recurrence is found, patient prognosis is poor (Fig. 4). Therefore the prevention of recurrence is important in patients with HCC. Postoperative adjuvant chemotherapy and/or immunotherapy may help in this regard. In recent patients, especially those with large tumors, we are trying aggressive adjuvant chemotherapy through a catheter indwelling in the hepatic artery, even after curative resection, to prevent recurrence or prolong the time until recurrence.

Recurrence occurs predominantly in the residual liver near the primary lesion, as shown in Figure 3. Although larger hepatic resection for primary HCC is recommended,

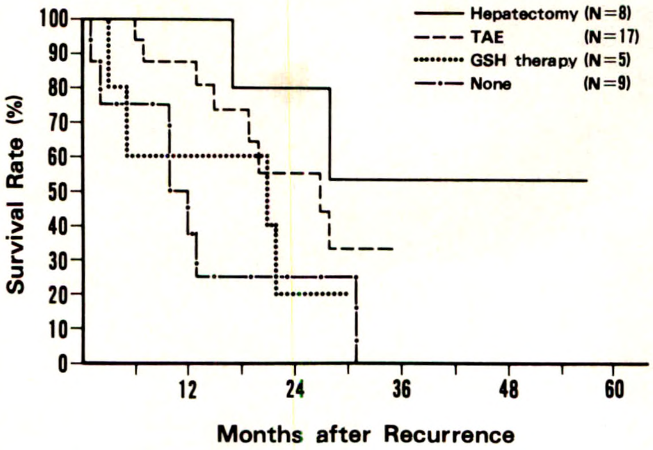


FIG. 5. Survival pattern according to type of treatment.

concomitant cirrhosis limits the resectable liver volume. A liver surgeon is like a tightrope walker, balancing between the fear of postoperative hepatic failure and the risk of recurrence. Total hepatectomy with hepatic transplantation may be an ideal treatment for HCC with severe cirrhosis. However results of hepatic transplantation for malignancies have not been satisfactory.[12,13] Postoperative use of immunosuppressants accelerates the recurrence of malignancy. However the reports of hepatic transplantation for malignancy have been from Western countries in which the features of HCC are very different from those in Asia, including Japan. As we showed in the previous study,[6] most HCC in Japan is detected during periodic examinations for chronic liver diseases, and the tumors are small ones that may be in the very early stages of development. Iwatsuki et al.[12] reported on 13 patients who underwent liver transplantation primarily for end-stage nonneoplastic liver disease but who had incidental HCC. Their results were excellent, and their patients' situations were similar to those of many patients with HCC in Japan. Total hepatectomy with liver transplantation may be the best way to treat patients with small HCCs and severely cirrhotic livers. We are now preparing a project on liver transplantation, an unexplored area in Japan.

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Elective Subtotal Splenectomy

Indications and Results in 33 Patients

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Elective subtotal splenectomy was performed in 33 patients (30 children and 3 adults) between 1981 and 1989. Indications for the procedure were (1) prevention of azathioprine-induced neutropenia (n = 20); (2) Type I Gaucher disease (n = 9); and (3) cholesteryl ester storage disease, chronic myelogenous leukemia, thalassemia major, and splenic cyst in one patient each. There were no operative deaths, no reoperations for bleeding, and 30 of 33 (91%) patients had a functioning splenic remnant documented by a postoperative radionuclide spleen scan. One patient developed neutropenia without evidence of viral infection that required temporary cessation of azathioprine and the patient with thalassemia major had only transient improvement in transfusion requirements. All other patients (94%) had control of the underlying condition for which the operation was performed. We conclude that subtotal splenectomy is a safe, effective therapy for a variety of nontraumatic conditions.

MANAGEMENT OF HYPERSPLENISM that is unrelated to primary hepatic disease traditionally has been treated by total splenectomy. The specter of postsplenectomy sepsis, particularly in children,[1-4] has made retention of splenic function desirable whenever possible. Although several series of partial splenectomies for trauma have been reported, this is the first large collection of elective partial splenectomy patients. The intent in almost all these patients was to control hypersplenism. Therefore more than 80% of the spleen was resected, hence the term subtotal rather than partial splenectomy. The techniques we used for subtotal splenectomy (STSx) were based on those developed for the management of traumatic splenic laceration.[5] This review assesses elective subtotal splenctomy in 33 patients during the last 8 years, with an emphasis on the long-term effects on these patients.

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Materials and Methods

Thirty-three patients underwent STSx. They can be divided into three groups: (1) patients awaiting renal transplantation who were at risk for developing azathioprine-induced neutropenia; (2) patients with Type I (adult, nonneuronopathic) Gaucher disease; and (3) other diseases requiring splenic resection.

Azathioprine-Induced Neutropenia

The patients determined to be at risk for azathioprine-induced neutropenia were between 9 months and 21 years of age. These 20 patients were awaiting renal transplantation and all had the procedure before our routine use of cyclosporine in 1984. One patient previously had lost a living related donor kidney to rejection when azathioprine was stopped because of refractory neutropenia.

Patients were considered to be at risk to develop neutropenia while on azathioprine if they demonstrated the following signs while on dialysis awaiting renal transplantation: (1) chronic neutropenia, white cell count less than 5000; (2) mild neutropenia, white cell count of 5000 to 6000, with other signs of hypersplenism, *i.e.*, thrombocytopenia or excessive transfusion requirements; or (3) mild neutropenia with an abnormal cortisol stimulation test.[6]

Gaucher Disease

Nine patients had STSx for type I Gaucher disease. Gaucher disease is an autosomal recessive genetic disorder

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caused by a deficiency of the enzyme glucocerebrosidase. The result is the accumulation of glucocerebroside predominantly in the reticuloendothelial system and the bone marrow.[7] Massive splenomegaly with hypersplenism is a common complication of type I Gaucher disease (Fig. 1). Type I is the most common of the three types of Gaucher disease. Type I is non-neuronopathic, usually diagnosed in adulthood, and generally the patients enjoy a normal life span. Type I patients diagnosed as children commonly have more severe disease than those diagnosed as adults. Children often suffer growth retardation, poor nutritional status, and frequent bone infarction crises. Six of our nine patients were 20 years old or younger.

Subtotal splenectomy was offered only to those who would have been considered for total splenectomy in the past. Indications for surgery were: (1) severe hypersplenism as evidenced by white cell counts less than 4000, hemoglobin level less than 9 g, or platelet count less than 50,000; or (2) severe symptoms due to the massive splenomegaly, such as orthopnea, or recurrent pain due to splenic infarcts. Recurrent spontaneous epistaxis or gastrointestinal bleeding was a major complaint in seven of the nine patients.

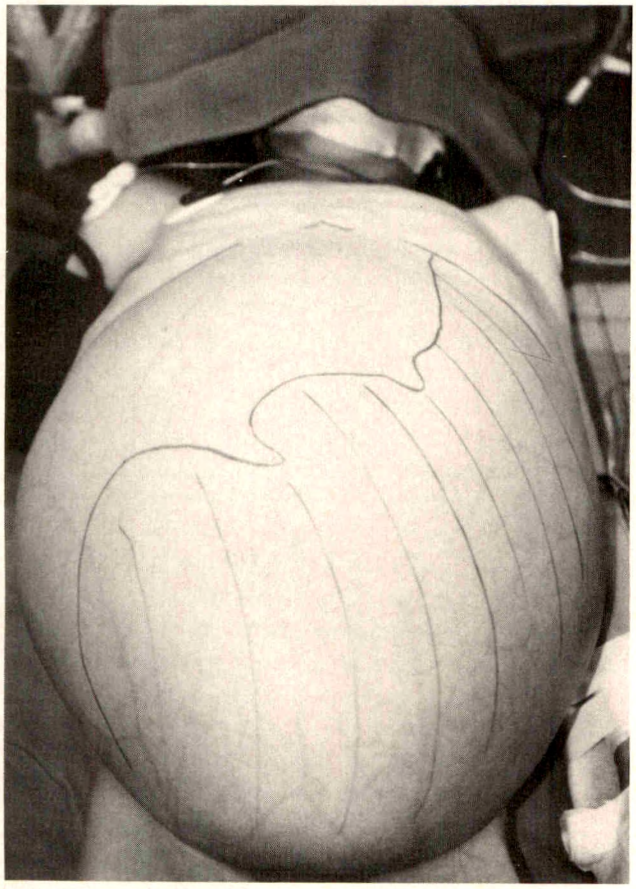

FIG. 1. Ten-year-old patient with type I Gaucher disease. Palpable splenic margins outlined on the abdominal skin.

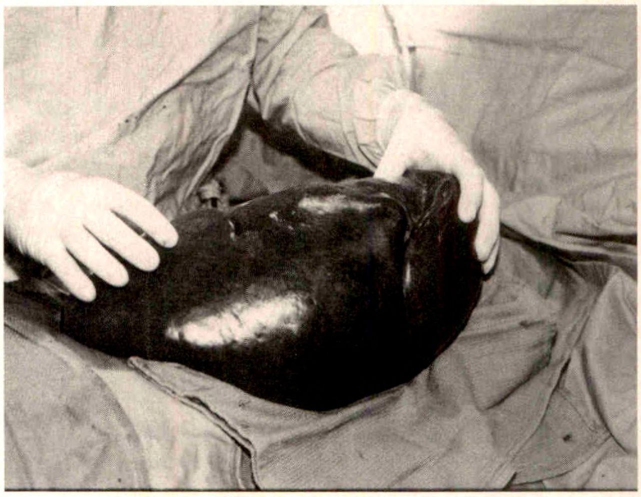

FIG. 2. Twenty-five-year-old patient with type I Gaucher disease. Intraoperative photograph showing mobilization of splenic attachments before ligation of splenic vascular branches.

Other Diseases Requiring Splenic Resection

Four children had STSx for the following diagnoses: (1) cholesteryl ester storage disease resulting in severe hypersplenism and splenic infarcts; (2) chronic myelogenous leukemia with severe splenic infarct pain unresponsive to conventional therapy with chemotherapy or radiation; (3) thalassemia major with increasing transfusion requirements and; (4) post-traumatic splenic cyst with chronic left upper-quadrant pain.

Surgical Technique

All patients received pneumococcal vaccine before surgery and were given perioperative antibiotics. The objective in all patients, with the exception of the one with a splenic cyst, was removal of 80% to 90% of the functioning splenic mass. The size of the splenic remnant retained varied depending on the size of the patient, the size of the spleen, and the underlying disease process. In the patients with massive splenomegaly, which includes all patients with Gaucher disease, the remaining splenic remnant was approximately the size of a man's fist. In this group 90% of each spleen was removed.

The technique for STSx has been described elsewhere.[8] Briefly, the spleen is dissected free from all attachments except the splenic artery and vein and is brought through the incision onto the anterior abdominal wall (Fig. 2). The vessels usually divide into three main branches before entering the splenic parenchyma: a moderate-sized superior branch that supplies 20% to 25% of the spleen, a large central branch that supplies 60% to 70% of the spleen, and a small inferior branch that supplies 10% to 20% of the splenic mass. This vascular arrangement makes it easiest, in most instances, to preserve the inferior portion of the spleen on its vascular pedicle.

Once the vessels supplying the segment to be resected have been dissected and ligated (Fig. 3), transection of the splenic parenchyma is accomplished using electocautery. Digital occlusion of the vessels supplying the viable remnant minimizes blood loss during transection. In those patients with platelet counts less than 50,000, platelets are administered after the segment to be resected has been devascularized and while the spleen is being transected. The dose of platelets is one pack per 5 kg of body weight, with a maximum of 10 platelet packs in patients weighing more than 50 kg.

The raw splenic surface is compressed with mattress sutures of chromic catgut (0 chromic in massive splenomegaly and 00 chromic suture in smaller spleens) on a straight needle. Suture ligation with chromic of large transected branches on the raw surface may be necessary. Microfibrillar collagen (Avitene, Alcon Surgical, Ft. Worth, TX) and a viable omental patch are placed over the raw surface. It is important to fix the splenic remnant to the left diaphragm with two chromic sutures, to prevent torsion, taking care to orient the splenic vessels properly. No drains are used. All patients were maintained on ampicillin, or an alternate antibiotic if they were allergic to penicillins, for several months after surgery. The length of time on prophylactic antibiotics varied according to patient age and diagnosis.

Results

There were no operative deaths and no patients required reoperation for bleeding or for infarction of the splenic remnant.

Azathioprine-Induced Neutropenia (Table 1)

Nineteen of the 20 patients had a functioning splenic remnant documented by a postoperative spleen scan. The one patient without a functioning remnant was operated on early in our experience and the remnant was not sutured to the left diaphragm. A functioning remnant was seen on spleen scan six days after operation but the patient developed left upper-quadrant pain and a left pleural effusion two days later and subsequently no remnant could be detected by scan. It is presumed that the remnant underwent torsion and infarction. Fixation of the splenic remnant to the left diaphragm became a routine part of the procedure after this complication occurred.

Seven patients had the STSx while undergoing another intra-abdominal procedure, five with bilateral nephrectomies, and two with cholecystectomies for cholelithiasis. Thirteen patients had STSx without an associated procedure. There were four complications. One splenic remnant infarct associated with fever and left pleural effusion, as mentioned above, resolved spontaneously. Two small-bowel obstructions occurred in patients having had bilateral nephrectomies at the same time as STSx; both required laparotomy and lysis of adhesions. One patient developed an incisional hernia that was repaired after kidney transplantation.

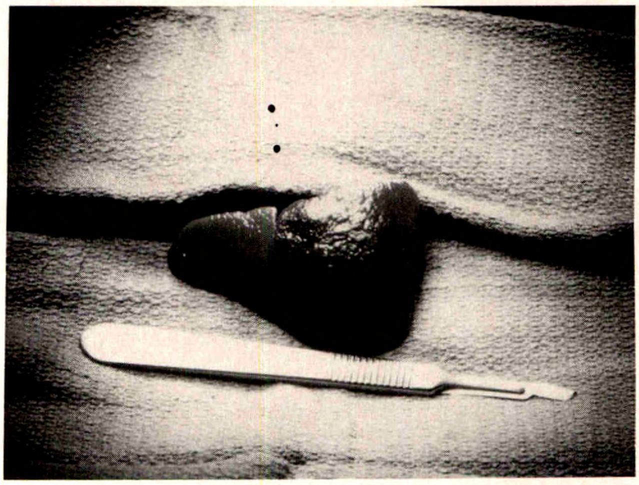

FIG. 3. Nine-month-old patient with renal failure at risk for azathioprine-induced neutropenia. Intraoperative photograph showing line of demarcation between viable (left) and nonviable splenic segments after ligation of the blood supply to the superior 80% of the spleen.

Nineteen of the 20 patients have undergone renal transplantation. Seventeen (85%) patients are alive and eight (47%) of those alive have functioning kidney allografts. All patients, except one, are more than 4 years beyond the date of their transplant. Six of the eight patients with functioning kidneys had living related donors and two had cadaver kidneys transplanted.

Six of seven patients receiving living related donor (LRD) transplants have functioning allografts, but one patient (patient 2) required four transplants to obtain a good result. Five of the LRD recipients received donor-specific blood or leukocyte transfusions before transplantation. Two of 12 patients receiving a cadaver donor kidney more than 4 years ago and treated with prednisone and azathioprine for immunosuppression have a functioning renal transplant. These results are not significantly different from those in children undergoing renal transplant at the same time in our hospital who were determined to not be at risk for azathioprine-induced neutropenia. The allograft function rate might well have been greater; however three of our adolescent patients purposely stopped their immunosuppressive medication and lost their kidneys to rejection.

Three patients required temporary cessation of their azathioprine after transplantation because of neutropenia (white cell count less than 4000). Two of the patients had documented cytomegalovirus (CMV) infection at the time of neutropenia and after recovery from the CMV illness they were returned to their preillness dose of azathioprine.

TABLE 1. *Subtotal Splenectomy Patients with Azathioprine-Induced Neutropenia*

Patient	Age (Years)	Concurrent Procedure	Viable Remnant	Kidney Donor	Complication	Follow-up		
						Neutropenia	Sepsis	Current Status
1	20	None	Yes	Cadaver	None	No	No	On dialysis; kidney Tx rejected at 1 year
2	9	None	Yes	Cadaver X2 LRD X2	None	No	No	Functioning transplant; on cyclosporine at 1 year. Previous Txs lost to rejection
3	7	Cholecystectomy	Yes	Cadaver	None	No	No	On dialysis; kidney Tx rejected at 3 years
4	11	None	Yes	Cadaver	None	No	No	On dialysis; kidney Tx rejected at 2 years
5	14	None	Yes	Cadaver	None	Yes—with CMV infection	No	On dialysis; kidney Tx rejected at 4 years
6	0.75	None	Yes	Cadaver X2	None	No	No	Died; Primary nonfunction of both Txs, died of renal failure
7	14	None	Yes	Cadaver	None	No	No	Died; Liver failure due to chronic active hepatitis, nonfunction of Tx
8	12	None	Yes	Cadaver	None	No	No	On dialysis; lost graft after 2 years due to medication noncompliance
9	16	None	Yes	None	None	No	No	On dialysis
10	15	None	Yes	LRD	None	No	No	Functioning transplant—5 years
11	13	None	Yes	LRD	None	No	No	On dialysis; lost graft after 4 years due to medication noncompliance
12	13	Bilateral nephrectomy	Yes	Cadaver	Small-bowel obstruction	No	No	On dialysis; lost graft after 2 years due to medication noncompliance
13	12	Bilateral nephrectomy	No	LRD	Infarcted remnant & L pleural effusion	No	No	Functioning transplant—6 years
14	3	Cholecystectomy	Yes	Cadaver	Incisional hernia	No	No	Died; good graft function for 2 years, died of hypertensive encephalopathy
15	12	Bilateral nephrectomy	Yes	Cadaver	None	Yes—with CMV infection	No	On dialysis; good graft function for 2 years, lost graft to chronic rejection
16	11	None	Yes	LRD	None	Yes—2 episodes	No	Functioning transplant—6 years
17	17	Bilateral nephrectomy	Yes	Cadaver	Small-bowel obstruction	No	No	Functioning transplant—4 years
18	16	None	Yes	LRD	None	No	No	Functioning transplant—6 years
19	21	None	Yes	LRD	None	No	No	Functioning transplant—7 years
20	2	Bilateral nephrectomy	Yes	Cadaver X2	None	No	No	Functioning transplant—5 years 1st Tx lost to renal artery stenosis

Tx, transplant.
CMV, cytomegalovirus.
LRD, living related donor.

One patient had two episodes of neutropenia without evidence of CMV infection that required a temporary decrease in the dosage of azathioprine. One patient was transplanted early in our cyclosporine experience and one was never transplanted, thus neither received azathioprine. Of the 18 patients at risk for azathioprine-induced neutropenia, one (6%) developed neutropenia without evidence of viral infection.

Gaucher Disease (Table 2)

Eight of nine patients have a functioning splenic remnant documented by postoperative spleen scan. It is noteworthy that two of the eight patients with splenic function did not show radionuclide uptake within the first postoperative week, although subsequently splenic remnant uptake was demonstrated at 3 and 6 months after surgery. Pitted red cell counts, another measure of splenic function, were performed after operation in eight patients and were in the normal range (less than 1%) in seven patients. The one patient with a nonfunctioning remnant had a pitted red cell count of 0.8% and is likely to have some residual splenic function that is not yet detectable by scan. One patient with a functioning remnant with areas of infarction had a count of 8.6%. All patients had dramatic improvement of hypersplenism and the symptoms related to splenomegaly.

A small pleural effusion developed in four patients and was associated with a temperature elevation of 38.5 C to 39 C. These effusions resolved without thoracentesis in each case and did not delay discharge. One patient developed abdominal wall cellulitis that required IV antibiotic therapy for 1 week and remained hospitalized for 12 days. This was the only patient in this group hospitalized for more than eight days.

In the first year after STSx, four children had bone pain episodes consistent with bone infarct crises. Three of these patients had had similar symptoms before surgery, but the frequency and severity of the episodes increased after the operation. One patient had an episode of bilateral tibial pain after minor trauma, one patient had a single episode of polyarticular arthritis, and another had two episodes of gout after surgery.

The first patient with STSx for Gaucher disease had the procedure 5 years ago. The splenic remnant has approximately doubled in size (Figs. 4A and B), but the patient's hypersplenism remains controlled. In all patients the remnant has increased in size but much less so in the adults than in the children. No patients have shown signs of hepatic dysfunction due to increased glucocerebroside deposition in the liver. Eight of the nine patients, including the one without splenic function, considered themselves much improved after surgery.

These patients have massively enlarged spleens that usually comprise more than 10% of their body weight compared to the normal spleen-to-body weight ratio of 0.3%. Although it is difficult to quantify the relief that these patients experience once the STSx has been done, it is clear that improved muscle mass, appetite, and energy level consistently develop after surgery. In patients with growth potential, two of four had a significant growth spurt within 1 year of STSx.

Other Diseases Requiring Splenic Resection (Table 3)

In the last and less specific category, three of four patients have a functioning splenic remnant. The patient with chronic myelogenous leukemia and multiple splenic infarcts had no evidence of splenic function after surgery and died of recurrent leukemia 1 month after surgery. The patient with cholesteryl ester storage disease had significant improvement of her hypersplenism but continues to suffer from severe liver disease. The patient with thalassemia major had temporary improvement of his transfusion requirements, but within 1 year had returned to his preoperative transfusion needs. The patient with the post-traumatic splenic cyst has a viable splenic remnant and is asymptomatic.

Discussion

It is well known that the spleen has both hematologic and immunologic functions. With the exception of the fetus and certain disease processes, the human spleen does little to generate new blood cells. The primary hematologic function of the spleen is to act as a sophisticated filter to delete from the circulation those erythrocytes, leukocytes, and platelets that are seen as flawed. The hypersplenic state is due to excessive sequestration of the blood cells resulting in cytopenias in the peripheral circulation. Hypersplenism is usually associated with splenomegaly.[9] The immunologic function of the spleen is complex but, on a very basic level, is designed to clear encapsulated bacteria and parasites, generate a cellular response to infection, and initiate antibody formation. The spleen is also very active in the nonself antigen-recognition pathways activated by allograft transplantation.

Splenectomy was commonly used as a nonspecific immunosuppressive technique in patients awaiting renal transplantation in the 1960s and 1970s. Reports of unimproved allograft function and definite increased mortality rate from infection, particularly in children, in those having had splenectomy[10–13] have eliminated the procedure from the pretransplantation preparation of these patients.

Hypersplenism occurs in about 10% of hemodialysis patients.[14] The cause of azathioprine-induced neutropenia after renal transplantation is probably a combination of bone marrow suppression and increased splenic seques-

TABLE 2. *Subtotal Splenectomy Patients with Gaucher Disease*

		Hgb (gms)		WBC ×10³		Platelets ×10³				Follow-up			
Patient	Age (Years)	Pre	Post*	Pre	Post*	Pre	Post*	Viable Remnant	Complication	Pitted RBC's %†	Bone infarcts	Solenic Remnant	Current Status
21	7	9.1	11.0	3.9	4.8	47	142	Yes	Left pleural effusion	0.2	Yes—multiple	Doubled in size in 4.5 years	Significant problems with bone infarcts, no hypersplenism. Developed nephrotic syndrome; 5 years postop.
22	10	7.0	10.1	3.7	14.1	123	279	No—1 month Yes—3 months	Left pleural effusion	8.6	Yes—multiple	No change in size in 4 years Infarcts present	No hypersplenism, many orthopedic problems; 4 years postop.
23	20	7.8	11.1	1.8	6.6	35	149	Yes	Left pleural effusion	0.2	1 episode of bilateral tibial pain following trauma	33% larger at 6 months, slightly larger at 3 years	Excellent; 4 years postop.
24	48	6.0	12.1	2.7	5.5	29	123	Yes	None	0.3	1 episode of polyarticular arthritis	33% larger at 6 months, no increase at 3 years	Excellent; 4 years postop.
25	12	8.0	10.5	2.1	11.1	41	285	No—1 month Yes—6 months	Left pleural effusion	0.6	Yes—multiple	33% larger at 2 years then at 6 months Infarcts present	Less problems with bone infarcts after 1st year. Improved activity; 2 years postop.
26	38	8.0	10.2	2.9	8.2	62	151	Yes	None	0.2	No—2 episodes of great toe gout	33% larger at 1 year than at 1 month	Excellent; 2 years postop.
27	20	9.0	13.2	1.6	12.5	24	339	No—1 month No—2 years	Abdominal Wall Cellulitis	0.8	No	Not visible on scan	Excellent; 2 years postop.
28	17	9.3	11.5	2.2	6.5	52	199	Yes	None	0.2	Yes—1 episode of femur pain	Doubled in size in 1 year	Excellent; 2 years postop.
29	25	8.8	10.7	1.9	9.2	38	129	Yes	None	—	No	Only 1 scan done	Excellent; 3 months postop.

RBC, red blood cells.
* At the time of most recent visit (see current status).

† Normal pitted RBC % is less than 1%.

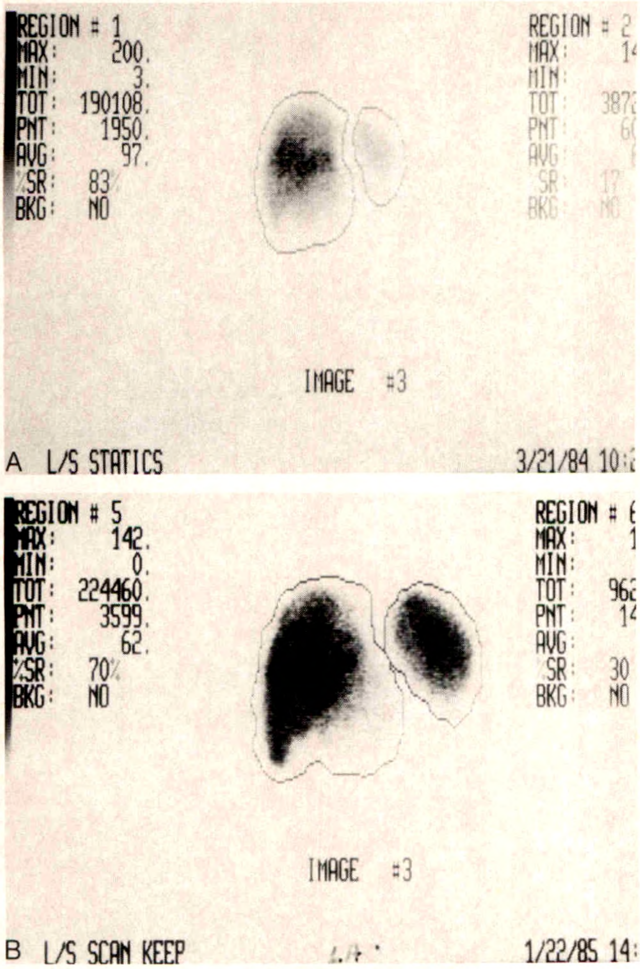

FIG. 4. Seven-year-old patient with type I Gaucher disease liver spleen scan at (A) 4 months and (B) 14 months after STSx, which demonstrates the increased size of the splenic remnant during that time.

tration of the neutrophils. It has been established that total splenectomy lessens the incidence of azathioprine-induced neutropenia.[15] Before 1981 approximately one third of our pediatric renal transplant patients had temporary cessation or reduction of their azathioprine dosage for neutropenia after transplantation. In 1981, because of this problem, we investigated partial splenic ablation by percutaneous embolization as described by Moses et al.[16] The development of postsplenic embolization syndrome,[16] which is similar to acute pancreatitis, in two of our five patients and the recurrence of the neutropenia in the two patients in whom partial splenic embolization initially appeared to be successful, encouraged us to seek a surgical solution to the neutropenia.[17]

The long-term outcome of the 20 patients undergoing STSx before renal transplant is not significantly different from those patients having a transplant without STSx during the same time period. It is impossible to say whether we improved the STSx group's allograft function by the procedure because we do not have a control group at risk for azathioprine-induced neutropenia whose members did not have STSx between 1981 and 1984. It is clear that the incidence of neutropenia without concurrent CMV infection (1 of 18 patients at risk [6%]) is substantially lower than rate we saw before 1981; however this low incidence of azathioprine-induced neutropenia apparently did not result in improved allograft survival rate.

It is encouraging that there have been no episodes of sepsis in the transplant patients with a 5-to-8-year follow-up, but the population may be too small or the follow-up period may be too short to safely conclude that they are not at increased risk for sepsis after STSx.

Hypersplenism due to Type I Gaucher disease has been treated traditionally by total splenectomy.[18] The first report of partial splenectomy for Gaucher disease appeared in 1980[19] and subsequent reports with short-term results have also appeared.[8,20,21] Partial splenic embolization has been used to treat hypersplenism due to Gaucher disease;[22] however we see no benefit to that technique over STSx because it has little effect on the splenic mass, which is the source of many patient complaints.

Our experience with nine Gaucher patients, eight of

TABLE 3. *Subtotal Splenectomy Patients with Other Diseases Requiring Splenic Resection*

Patient	Age (Years)	Diagnosis	Viable Remnant	Outcome
30	3	Chronic myelogenous leukemia	No	Tolerated subtotal splenectomy well. Died 1 month after discharge from leukemia relapse
31	11	Thalassemia major	Yes	Lessened transfusion requirements for 1 year, but thereafter returned to preoperative requirements
32	10	Cholesteryl ester storage disease	Yes	Hypersplenism improved Preop. Postop. WBC 2200 4100 Hgb 8.9 11.4 Platelets 74,000 156,000 2 years postop liver disease has progressed
33	14	Posttraumatic splenic cyst	Yes	Excellent; 6 years postop.

whom are alive more than 1 year after surgery, has given us certain insights that have not been previously emphasized. Although a review of 239 Gaucher disease patients concluded that splenectomy does not increase the risk of bone infarction,[23] it appears that children in the first decade of life with Type I Gaucher disease are particularly susceptible to bone infarcts after total splenectomy[24] and we have found a similar high incidence of bone infarcts in our children after STSx. This problem can be debilitating in some patients, particularly if the vertebrae are involved. Indications for STSx in the young child must be stringent because of the potential for these bone crises. Efforts to identify patients at risk for this problem before surgery are ongoing.

We believe that there is a specific salutary time period in which to perform STSx in patients with Type I Gaucher disease. The mere presence of a large spleen is not an indication for surgery; however prolonged delay may result in multiple painful splenic infarcts that make partial splenic preservation more difficult, and recurrent spontaneous hemorrhages requiring transfusions. In children there may be improvement in growth after STSx, which must also be taken into consideration. The optimal time for surgery in both adults and children is when symptoms increase in frequency and severity and before large segments of the spleen become infarcted.

The question of the ultimate fate of the splenic remnant in the Gaucher disease patient remains unanswered. Clearly at 5 years there is significant regrowth of the remnant, but the hypersplenism remains in check. Again there seems to be a difference between children and adults, with the remnant increasing in size more quickly in the children than in the adults. Adults followed for more than 3 years have shown only a 30% increase in remnant size. It is conceivable that another STSx may be necessary in some of these patients in the future. Management of Gaucher disease patients, particularly children, must take into consideration that the STSx is only palliative treatment for hypersplenism and any procedure must not interfere with future treatments such as enzyme replacement or bone marrow transplantation[25] directed at the underlying enzyme deficiency.

Partial splenectomy is the procedure of choice for a splenic cyst, regardless of whether the cyst is of congenital, traumatic, or infectious origin.[26–28] The child with cholesteryl ester storage disease[29] was similar to the patients with Gaucher disease in indications for surgery; however she also had severe cirrhosis and portal hypertension. Although we would not recommend routine STSx for hypersplenism due to portal hypertension, the patient clearly shows that the procedure can be performed safely under those circumstances. Successful management of hypersplenism due to portal hypertension by partial splenic embolization has been reported.[30]

The patient with chronic myelogenous leukemia had a very unsatisfactory course. Not only did he fail to show a viable splenic remnant, he died of leukemia relapse 1 month after surgery. He was considered a candidate for surgery only after chemotherapy and radiation to the spleen were unsuccessful in managing constant, severe splenic pain. Results with total splenectomy in this form of leukemia are also poor because of the limited life expectancy for these patients.[31]

Thalassemia major has been treated by total splenectomy when transfusion requirements become excessive. Our patient was an 11-year old who was receiving two to three units of blood every 2 weeks. After STSx he required three units of blood every 2 months, but within 1 year he needed his preoperative transfusion requirements. His parents refused further surgical therapy. We removed approximately 80% of the spleen and we believe that a greater amount of spleen should be resected for this disease. Partial splenic embolization has been used in thalassemia major.[32]

The technique we used for STSx has remained essentially unchanged during the 8-year period. Others have advocated the use of the laser[33] or the ultrasonic dissector[34] for splenic transection. The raw splenic surface has been covered with fibrin glue[35] or a mesh of absorbable suture.[36,37] We believe these are acceptable alternatives but not necessarily improvements on a technique that has proved completely safe and effective in our hands.

From experimental studies it is clear that maintenance of some sepsis protection after STSx requires retention of the splenic artery and vein as the blood supply to the remnant,[38,39] and at least 25% of the original normal-sized spleen.[40,41] We tried to resect 80% or more of the spleen because that amount is necessary to control the hypersplenic state. In those patients with massive splenomegaly due to an infiltrative process, it is difficult to estimate how much spleen must be left for sepsis protection because the spleen is so distorted and the remnant is not composed entirely of normal spleen. We have chosen to leave a remnant no larger than 8 cm × 8 cm × 5 cm, even when the spleen occupies the majority of the abdominal cavity. To date we have seen no episodes of sepsis in these 33 patients, 27 of whom are alive 4 or more years after their STSx.

The safety and effectiveness of STSx has been conclusively demonstrated for a variety of nontraumatic conditions by this series of patients. In addition careful patient selection and attention to surgical technique, particularly in those patients with massive splenomegaly, offers excellent and long-lasting control of hypersplenism in a variety of nontraumatic conditions.

Acknowledgments

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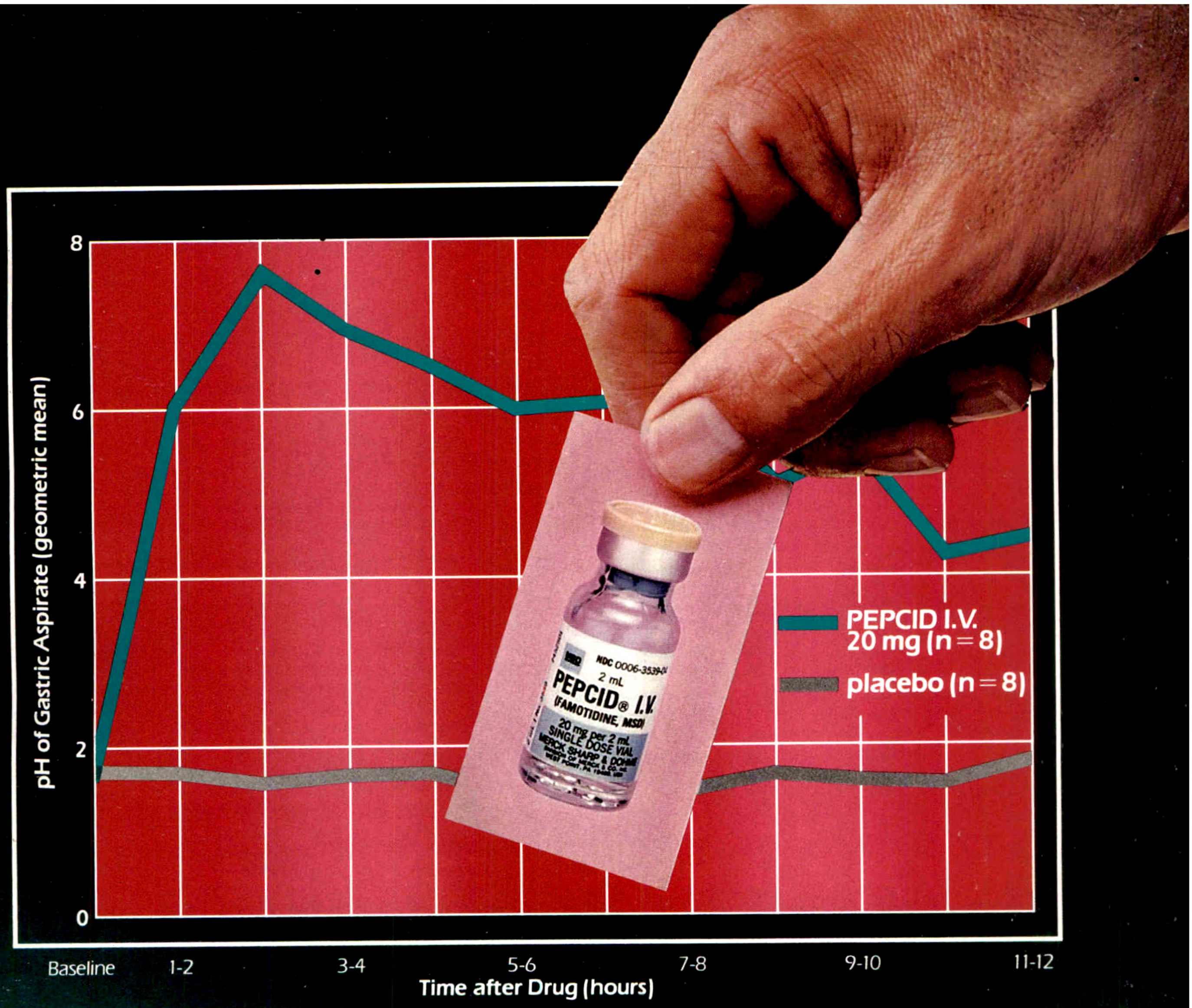

A double-blind, placebo-controlled study[1] involving eight volunteer hypersecretor subjects. The pH of gastric aspirates was measured hourly for 12 hours following single intravenous doses. PEPCID I.V. maintained the mean gastric pH above 4.0 at all time points throughout the 12-hour period with one 20-mg I.V. dose.

[1] Ryan, J.R. et al.: Comparison of effects of oral and intravenous famotidine on inhibition of nocturnal gastric acid secretion, Am. J. Med. 81 (Suppl. 4B): 60-64, October 24, 1986.

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Information for Patients: The oral suspension should be shaken vigorously for 5 to 10 seconds prior to each use, and unused constituted oral suspension should be discarded after 30 days.

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Carcinogenesis, Mutagenesis, Impairment of Fertility: In rats and mice given oral doses up to approximately 2,500 times the recommended human dose for active duodenal ulcer, there was no evidence of carcinogenic potential; at these doses in rats, fertility and reproductive performance were not affected. No evidence of a mutagenic effect was observed.

Pregnancy: *Pregnancy Category B*—There are no adequate or well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether famotidine is secreted into human milk; however, it is secreted into the milk of lactating rats. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: No dosage adjustment is required based on age but may be necessary in severe renal impairment (see Clinical Pharmacology section of Prescribing Information).

Adverse Reactions: The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2,500 patients. In the placebo-controlled clinical trials, the incidence of adverse experiences with PEPCID Tablets 40 mg at bedtime was similar to that with placebo.

Incidence Greater than 1%: The following adverse reactions have been reported to occur in more than 1% of patients on therapy with PEPCID in controlled clinical trials and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%), and diarrhea (1.7%).

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AV block has been reported with other H_2-receptor antagonists, but not with famotidine.

Management of Overdosage: There is no experience to date with deliberate overdosage. Up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

Dosage and Administration: ***Duodenal Ulcer:*** The recommended adult oral dosage for active duodenal ulcer is 40 mg h.s.; most patients heal within 4 weeks, and it is rarely necessary to use the full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective. For maintenance therapy, the recommended oral dosage is 20 mg h.s.

Benign Gastric Ulcer: The recommended adult oral dosage for active benign gastric ulcer is 40 mg h.s.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas): The dosage varies with the individual patient; the recommended adult oral starting dosage is 20 mg q6h, but some patients may require a higher starting dosage. Dosages should be adjusted to individual patient needs and continued as long as clinically indicated; up to 160 mg q6h have been administered to some patients with severe Zollinger-Ellison syndrome.

Oral Suspension: The oral suspension may be substituted for tablets.

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Intravenous Administration: In some hospitalized patients with pathological hypersecretory conditions or intractable ulcers or in patients who are unable to take oral medication, the recommended intravenous dosage is 20 mg q12h. For preparation of intravenous solutions for injection or infusion and for compatible diluents, please see Prescribing Information. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

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Liver Transplantation for the Budd-Chiari Syndrome

GLENN HALFF, M.D., SATORU TODO, M.D., ANDREAS G. TZAKIS, M.D.,
ROBERT D. GORDON, M.D., and THOMAS E. STARZL, M.D., PH.D.

A retrospective study was performed that analyzed 23 patients who had an orthotopic liver transplantation for the Budd-Chiari syndrome with end-stage liver disease. Patient follow-up was as long as 14 years. The technical considerations relevant to the Budd-Chiari syndrome were discussed. There have been no serious complications of postoperative anticoagulation. Three patients, all of whom died, had recurrence of the Budd-Chiari syndrome. No other patient has had evidence of recurrent Budd-Chiari syndrome on postoperative liver biopsies. One-, 3-, and 5-year actuarial survival was 68.8%, 44.7%, and 44.7%, respectively. It was concluded that orthotopic liver transplantation is the most effective treatment for patients with the Budd-Chiari syndrome and end-stage liver disease.

From the Department of Surgery, University Health Center of Pittsburgh, University of Pittsburgh, and the Veterans Administration Medical Center, Pittsburgh, Pennsylvania

THE BUDD-CHIARI SYNDROME is a poorly defined spectrum of disease ranging from a veno occlusive disorder with small vessel occlusion to thrombosis of the major hepatic veins and/or inferior vena cava. A wide variety of underlying disorders and risk factors such as paroxysmal nocturnal hemoglobinuria (PNH), polycythemia vera and other myeloproliferative diseases, tumors, amoebic abscesses, congenital venal caval webs, oral contraceptives, and pregnancy have been reported to cause the syndrome, although most cases of the syndrome have been attributed to cryptogenic causes.[1,2] More recently antithrombin III deficiencies, lupus anticoagulants, and occult myeloproliferative diseases have been suggested to comprise a part of the cryptogenic category.[3-5] Attempts at treatment have included anticoagulation, thrombolysis, portasystemic shunts, and liver transplantation. Although liver transplantation removes the cirrhotic liver disease, it may not cure the underlying thrombotic disorder. Recurrence of Budd-Chiari lesions in a transplanted liver has been previously described.[6] In an additional report of 17 patients from Cambridge who had liver transplants for Budd-Chiari, only one patient who was on anticoagulation therapy had a late death that may have been related to the underlying thrombotic disorder.[7] We have described another large group of patients who have had liver transplants for end-stage liver disease secondary to the Budd-Chiari syndrome to discuss the long-term prognosis, to report the results of postoperative anticoagulation therapy, and to describe the technical problems associated with this disease.

Materials and Methods

Patients

Twenty-three patients were transplanted for the Budd-Chiari syndrome between 1974 and 1988. The transplants performed before 1981 were performed at the University of Colorado Medical Center in Denver, Colorado, and those after 1981 were performed at the Presbyterian-University Hospital in Pittsburgh, Pennsylvania. This represented 1.3% of patients undergoing liver transplantation during this time period. The diagnosis was confirmed by postresection pathologic examination in all patients. The ages at time of transplantation varied from 13 to 48 years, with a median age of 30 years. Three patients were male and 20 were female.

The patients were diagnosed with the Budd-Chiari syndrome an average of 2.3 years (SD ± 2.7 years) before their transplants. The underlying etiologies (Table 1) included paroxysmal nocturnal hemoglobinuria in 1, polycythemia vera in 3, essential thrombocytosis in 1, and

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TABLE 1. *Summary of Patient Data*

OLTx No.	At Op.	OLTx	Etiology	Status	Comments
92	22	11/28/74	Polycythemia vera	Alive	No anticoagulation, 2 children post-transplant, liver biopsy 1986 normal
174	20	3/25/80	Oral contraceptive lupus anticoagulant thrombocytosis		Died 6/81 multiple thrombotic postoperative events without anticoagulation, no thrombotic events for 1 year on anticoagulation; recurrent Budd-Chiari when anticoagulation stopped for a procedure
179	21	6/5/80	Oral contraceptive	Alive	No anticoagulation, no thrombotic events
181	16	8/23/80 3/17/82 3/25/82	Unknown	Died 4/82	Retransplanted for chronic rejection, no recurrent Budd-Chiari, died of candidiasis
270	28	12/11/82	Oral contraceptive	Died 1/83	Aspergillus pneumonia
371	31	3/18/84	Unknown	Died 1/87	Died from recurrent Budd-Chiari; one episode of subtherapeutic anticoagulation
385	40	4/20/84	Unknown	Alive	Liver biopsy 4/86 normal
511	22	4/4/85	Oral contraceptive	Alive	Hepatic artery thrombosis 9/85, subtherapeutic anticoagulation, not retransplanted
624	35	10/9/85	Polycythemia vera; oral contraceptive	Died 12/85	Pseudomonas pneumonia
733	38	3/2/86	Polycythemia vera	Died 3/86	Candidiasis
735	36	3/4/86	Unknown	Died 4/86	Cecal perforation
736	13	3/4/86	Cysteamine	Alive	No anticoagulation, no thrombotic events
919	40	10/12/86	Unknown	Alive	Liver biopsy 2/87, normal
1151	30	7/4/87	Unknown	Alive	
1230	35	9/13/87	Essential thrombocytosis	Died 11/87	Pseudomonas pneumonia
1247	25	9/25/87	Oral contraceptive	Died 9/87	Intraoperative death from pulmonary emboli
1281	29	10/31/87 11/1/87 11/5/87	PNH	Died 11/87	OLTx #1: primary nonfunction OLTx #2: thrombosed hepatic artery OLTx #3: thrombosed hepatic and portal vein, Aspergillus in thrombus artery
1478	48	4/12/88	Unknown	Alive	
1487	25	4/19/88	Oral contraceptive	Alive	
1693	21	9/9/88	Oral contraceptive	Alive	
1709	35	9/22/88 9/24/88	Unknown	Alive	OLTx #1: primary nonfunction
1755	42	10/30/88	Unknown	Alive	
1774	32	11/10/88	Lupus anticoagulant	Alive	

OLTx, orthotopic liver transplantation. PNH, paroxysmal nocturnal hemoglobinuria.

cysteamine administration for the treatment of cystinosis in 1. Seven of the patients had a significant history of oral contraceptive use. Two of these patients had an antithrombin III deficiency and two had a protein C deficiency, but each of these had an accompanying deficiency of other coagulation factors that made a decrease in hepatic synthetic function the likely cause. Two patients had associated lupus anticoagulants. The cause in the remaining nine (39%) patients was cryptogenic.

The patient with PNH was diagnosed 10 years before symptoms of end-stage liver disease began. The patients with myeloproliferative disorders were diagnosed 6 years before liver disease became clinically significant in 1, during the work-up for Budd-Chiari syndrome, which was 1 year before operation, in 1, and 7 years after operation in 1 patient who had no known cause at the time of transplantation.

The Budd-Chiari syndrome was initially diagnosed by clinical presentation and a liver biopsy with or without a venogram in 74%, and only by a venogram in 26%. An ultrasound added diagnostic confirmation in 14 of 15 (93%) of the patients in whom it was used.

In more recent patients the venogram was not performed unless there was a diagnostic question after liver biopsy and ultrasound had been performed. Nuclear magnetic resonance imaging has added additional confirmation in all eight patients it was used on during the last 2 years.

Five of the patients had a history of previous portal caval shunts and four had had peritoneal venous shunts placed. Three patients had been treated unsuccessfully with anticoagulants and thrombolysis. Prior thrombotic events had occurred in 3 patients (a deep venous thrombosis in 1, a pulmonary emboli in 2, 1 of whom required thoracotomy and embolectomy, and a sagittal sinus thrombosis in 1). The sagittal sinus thrombosis presented as a severe headache.

Indications for orthotopic liver transplantation included end-stage liver disease with intractable ascites in 52%, recurrent variceal bleeds in 43%, encephalopathy in 47%, spontaneous bacterial peritonitis in 9% and hepatorenal failure in 34%. One of the patients was intubated in the intensive care unit and was placed on vasopressors immediately before transplantation. The decrease in synthetic function of the liver was not as severe as that in many other causes of end-stage liver disease. The average prothrombin time was 14.9 seconds (SD ± 0.7), the average bilirubin was 4.3 mg/dL (SD ± 3.2), and the average albumin was 2.8 am/dL (SD ± 0.69).

Technical Considerations

At operation 30% of the patients were found to have dense adhesions between the liver and diaphragm surrounding the suprahepatic inferior vena cava (IVC). Almost all of the patients had severe portal hypertension. The dissection was usually very difficult due to the large liver size and typically enlarged caudate lobe. The average liver volume on preoperative Cat scan was 2441 cc (SD ± 752 cc). Portal bypass was usually instituted early in the operation before most of the liver dissection to decrease the blood loss related to the severe portal hypertension. In some cases the connective tissue around the suprahepatic IVC was so dense that it could not be safely encircled to apply a clamp. In these cases the infrahepatic IVC was ligated and oversewn and the liver was then dissected in a retrograde fashion up to the suprahepatic inferior vena cava, as has been previously described,[8] with the remainder of the operation preceding in the standard fashion.[9] The suprahepatic vena caval cuff was fashioned in some cases by dissecting superiorly up to the right atrium. This was done through the diaphragm (Fig. 1). A thoracic extension was not necessary in any of the patients. The average intraoperative blood loss was 21.8 units (SD ± 17.6).

Anticoagulation

Most patients within the last 5 years were given dextran 40 at 20 cc/hour beginning immediately after operation and continuing for five days. Twenty-five hundred units of subcutaneous heparin BID was begun on postoperative day 1 if the prothrombin time was less than 18 seconds and there was no postoperative bleeding. When the patients' clinical courses were stable with no future plans for invasive procedures, the patients' were converted to Warfarin anticoagulation. This was done an average of 4.6 days (SD ± 6.2) after operation. Two patients who had early deaths and were never put on Coumadin

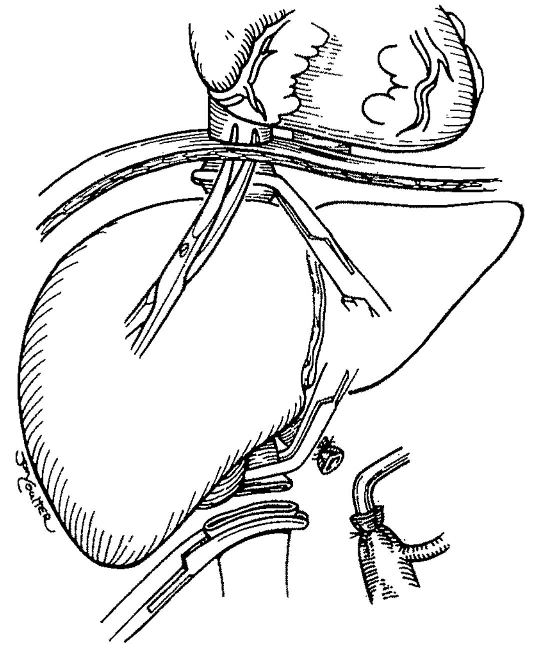

FIG. 1. Suprahepatic venal caval cuff construction by dissection through the diaphram.

(DuPont, Wilmington, DE) due to a coagulopathy were excluded from this calculation. When an invasive procedure such as a liver biopsy or operation was planned, the patients were converted to heparin anticoagulation with a partial thromboplastin time between 1.5 and 2 times control, which was stopped shortly before the procedure and restarted 6 hours after the procedure if there seemed to be no significant bleeding.

Results

Pathologic Findings In the Native Liver

Thrombosed main hepatic veins were found in the native liver pathologic specimens in 83% of the patients. Four (17%) also had nonocclusive thrombus in their IVC. One of these four livers had membranous webs in the retrohepatic IVC in addition to thrombosed hepatic veins and cirrhosis. Typical histologic findings were central lobular congestion and necrosis with dilation of the sinusoids, obliteration of central veins, varying degrees of central-to-central and central-to-portal bridging fibrosis, and organized thrombus in branches of the main hepatic veins.

Recipient Survival

Overall 16 of 23 (69.5%) of the patients survived the initial hospitalization, including all six operated on during 1988. One-, 3-, and 5-year actuarial survival was 68.8%, 44.7%, and 44.7%, respectively. This compared with 1-, 3-, and 5-year survivals of 69%, 61%, and 57.6%, respectively, in the age-matched population of all transplanted patients in the Pittsburgh–Denver experience. This difference did not achieve statistical significance using the generalized Wilcoxin (Breslow) Method. The *P* value was 0.50. Using this method, the patients transplanted within the last year were excluded from the calculation. Included were Colorado patients from the precyclosporine era in which 1-year overall survival in adults was approximately 25%.

Causes of Death

Causes of early death included Pseudomonas, Candida, and Aspergillus pneumonias, sepsis from a cecal perforation secondary to an ileus despite colonoscopic decompression, an intraoperative death from a massive pulmonary emboli and, in one patient, a thrombosed hepatic artery and portal vein. Late deaths were caused by systemic candidiasis after a retransplant for chronic rejection in one patient and recurrent Budd-Chiari in two patients.

Disease Recurrence

Recurrence of the Budd-Chiari Syndrome or postoperative thrombotic complications of the hepatic vessels occurred in three patients who were studied at autopsy. One patient suffered thrombosis of her hepatic artery and portal vein 1 week after operation. The thrombus in both grew aspergilli. This patient, with an underlying etiology of PNH, had thrombosed the hepatic artery in a previous graft four days after operation despite therapeutic levels of anticoagulation. In a second patient, the recurrent Budd-Chiari syndrome occurred acutely after Coumadin was held for a procedure without interim heparin therapy. On autopsy, more than 1 year after transplantation, the liver showed evidence of previous recurrent Budd-Chiari syndrome with fibrous occlusion of multiple central and sublobular hepatic veins, old thrombi in the hepatic artery and left renal vein, as well as recent thrombi in the portal vein, IVC, hepatic veins, and pulmonary artery. This patient had been started on Coumadin after transplantation after she had recurrent postoperative mesenteric thromboses with intestinal infarction, multiple pulmonary emboli, and thrombosis of the superior vena cava. She had remained asymptomatic on Coumadin for more than 1 year despite several subtherapeutic prothrombin times. An initial extensive evaluation did not show an etiology for her hypercoagulability and repeated evaluation just before stopping her Coumadin dosage for the procedure showed a thrombocytosis possibly related to a myeloid stem disease and a lupuslike inhibitor of the coagulation system. This patient has been previously reported.[6]

The third patient, who died from a recurrent Budd-Chiari syndrome, was therapeutically anticoagulated except for one four-day period 4 months before she was admitted with a fever and elevated liver enzymes. After admission she had a rapid clinical deterioration. On autopsy she was found to have severe old and recent intrahepatic hepatic vein thrombosis. The other vessels were patent. She had a cryptogenic etiology for her Budd-Chiari syndrome.

The patient who died of candidiasis after a retransplant for chronic rejection 1.5 years after her first transplant had no evidence of recurrent Budd-Chiari syndrome on pathologic exam of her first allograft.

Biopsy of the liver has been performed in a number of the patients after operation. Patient 93 had a liver biopsy 12 years after operation that showed no evidence of recurrence of Budd-Chiari despite not being treated with anticoagulation. She was diagnosed with polycythemia vera 7 years after transplantation. Patient 385 had a liver biopsy 2 years after operation that showed no evidence of recurrent Budd-Chiari. No other patient has had evidence of recurrent Budd-Chiari in a biopsy. However most of their biopsies were done within 1 month of transplantation.

Anticoagulation and Thrombosis

No patient has had a serious complication caused by anticoagulation. The patients' anticoagulation treatment has been followed closely either in the liver transplantation clinic or by their local physicians. The prothrombin times have been steadily maintained between 18 and 20 seconds with occasional drops to 15 and peaks to 24 seconds.

Postoperative thrombotic events occurred in the three patients previously mentioned and in two additional patients. One had a splenic vein thrombosis that led to variceal bleeding and was successfully treated with a splenectomy. This was the earliest patient with the longest follow-up, now 14.5 years. Her transplantation was on November 28, 1974.[10] She was not treated with anticoagulation medication. Another patient suffered thrombosis of her hepatic artery 5 months after operation. Her prothrombin time was 14 to 15 seconds at that time. She developed multiple hepatic abscesses and was treated with surgical drainage after refusing retransplantation. She is now doing well 4 years after the hepatic artery thrombosed.

Discussion

Budd-Chiari is a syndrome of decreased hepatic outflow caused by varying degrees of hepatic venous occlusion. It may present acutely with right upper quadrant pain, ascites, and hepatomegaly, or gradually over a period of months or years, with slowly increasing ascites and/or variceal bleeds. The liver becomes progressively more congested and the majority of untreated patients eventually die from the complications of end-stage liver disease.[11] In the study by Tavill et al.,[12] the mortality rate in 19 patients was 89%, with all 17 deaths occurring within 3.5 years of symptom onset.

Medical treatment with thrombolysis and/or anticoagulation has been successful in a small number of patients. Warren et al.[13] reported successful treatment with streptokinase in one patient with 4 months of follow-up. Greenwood[14] reported an initially successful outcome in one patient treated with urokinase who later rethrombosed and died of a variceal bleed 1.5 years later. Although there have been reports of successful thrombolytic therapy months after symptoms began,[15] thrombolysis usually works better if used soon after thrombosis has occurred. This is not practical in most Budd-Chiari patients because they generally present with a long history of symptoms. In Parker's study[11] only 20% of the patients presented with less than a 1-month history of symptoms. Powell-Jackson et al.[16] described streptokinase or heparin treatment in five patients with a 1-to-6 week history of symptoms. Treatment was successful in only one of the five patients and this patient was found to have cirrhosis on liver biopsy 10 years later. Her Budd-Chiari occurred secondary to trauma and she was treated with heparin. McDermott et al.[17] reported two patients with Budd-Chiari secondary to oral contraceptives who gradually improved with only anticoagulant treatment. Millikan et al.[18] described one patient who experienced recanalization of his hepatic veins after only diuretic treatment. This patient initially only had partial hepatic vein occlusion.

Surgical alternatives to treatment have included peritoneal venous shunts, portal-systemic shunts, and orthotopic liver transplantation. Peritoneal venous shunts have palliated the symptoms of massive ascites but have been unsuccessful in decreasing the mortality rate from the underlying progressive liver disease. Cameron[19] documented two patients who developed histologic liver fibrosis after being treated with working Leveen shunts, as well as one patient who died of liver failure with a Leveen shunt. Some of these patients survived for several years.

Surgical treatment with portal systemic shunts has been considered the treatment of choice in patients well enough to undergo surgery, although in some studies comparing medical and surgical treatment the groups were acknowledged not to be comparable, with the sickest nonoperable patients receiving medical treatment only. McCarthy[20] reported an 86% mortality rate after a mean survival of 6 months in 14 medically treated patients *versus* a 31% mortality rate in a very mixed group of 16 surgically treated patients with another four of the surgically treated patients having ongoing hepatic disease. In Ahn's study[21] of 30 patients, the 2-year survival rate in the medically treated group was 9%, *versus* 54% in the surgically treated group. This did not achieve statistical significance due to the small numbers, but a subgroup of surgically treated patients in which the IVC obstruction was also treated did have a significantly better survival rate (77% at 2 years). The number of different surgical procedures to treat Budd-Chiari has been reported to be as high as 23[21] and the results reported from different institutions have varied greatly. Inferior vena caval webs are common in the Orient and can often be treated with different types of membranotomy,[22] but this form of Budd-Chiari is very uncommon in the United States and was not represented at all in our series. The most commonly used procedures in the United States are the side-to-side portacaval shunt and the mesocaval shunt, when the IVC and portal vein are patent, and the mesoatrial shunt when the IVC is stenosed or thrombosed, with a patent portal vein. The mesocaval shunt has often been used when the enlarged caudate lobe made portacaval exposure very difficult.

The successful results with these surgical procedures range from 30% to 92%, with the majority having survival rates in the 60%-to-75% range. In Cameron's report[19] of 12 patients operated on for Budd-Chiari, two of five patients with mesocaval shunts did well with some improvement in sinusoidal congestion on postoperative biopsy. Of seven patients given mesoatrial shunts, three of seven were successful, but two of these three thrombosed and had to be redone. Of six patients who had portacaval shunts for Budd-Chiari reported in Milan,[23] two of six died of liver failure and four are alive at 6, 25, 27, and 29 months without encephalopathy. Ahn[21] had estimated

1- and 2-year survival rates with surgical treatment for Budd-Chiari of 61% and 54%. Vons[24] reported nine patients with Budd-Chiari; seven were treated with a mesocaval shunt and two with a portal-atrial shunt. One died and one was lost to follow-up, but the remaining seven are known to be alive without encephalopathy with a median follow-up of 23 months. The operative indications were ascites and right upper-quadrant pain. He reported that three of the patients had resolution of sinusoidal congestion on liver biopsy 1.5 to 2 years after operation.

Mitchell et al.[1] compiled a report of 27 patients in the literature who had side-to-side portacaval shunts. Only 30% survived and improved clinically for more than 1 year. This group included the six patients in Orloff's report, of whom five were alive after 8 months to 7 years without ascites or encephalopathy.[25] Follow-up biopsy in this group showed resolution of sinusoidal congestion with persistence of mild-to-moderate fibrosis. In some patients operated on before fibrosis was present on histologic examination, or in whom the fibrosis was mild, the congestion and sinusoidal dilatation resolved to a large degree on subsequent postshunt biopsies and the patients did well. In 1986 Orloff[26] reported a total of 13 patients treated with portacaval shunts for the Budd-Chiari Syndrome. Ninety-two per cent were alive without ascites with follow-up from 3 to 16 years. None of the patients had encephalopathy and 10 of the 12 were reported to have had return of normal liver function. The degree of preoperative liver disease was not described. Millikan et al.,[18] however, reported on the status of a patient 6 years after portacaval shunt for Budd-Chiari who was doing well but developed fibrosis with nodular regeneration on biopsy. This raises the question of the long-term progression of liver disease in patients who have portosystemic shunts. Five of our 23 (22%) recipients were treatment failures with this approach; their shunts were all widely patent.

In patients with end-stage liver disease manifested by cirrhosis on biopsy and by clinical symptoms, the treatment of choice, in our opinion, is orthotopic liver transplantation. The first successful orthotopic liver transplantation for Budd-Chiari was in 1974.[10] This patient is still alive and well and has had two children since her transplant. Campbell et al.[7] described 17 patients treated with orthotopic liver transplantation for the Budd-Chiari syndrome. They emphasized the importance of postoperative anticoagulant treatment and reported 1- and 3-year survival rates of 88% in the group that was anticoagulated. Their overall 1-year actuarial survival rate was 73%. Three additional patients died between 3 and 5 years after operation, one from liver failure whose portal vein had thrombosed 6 months after operation, one from lymphoma, and one from chronic rejection. Their indications for transplantation included transient encephalopathy in three patients, progressive encephalopathy in one patient, and a progressive downhill course in the rest.

In our own series the 1-, 3-, and 5-year actuarial survival rates were 68.8%, 44.7%, and 44.7%, respectively. This group of patients had many high risk problems, including previous failed shunt surgery, thrombosed portal veins, and severe portal hypertension. Most of the deaths have occurred during the initial hospitalization, most often from pneumonia and other forms of sepsis. There has been a trend of improvement with no deaths during the initial hospitalization in the six patients transplanted for Budd-Chiari during 1988.

There was a second mortality rate peak during the first 2 years after operation from thrombotic complications, but this was seen in the earlier years of the study and was at least partially due to anticoagulant management.

The technical aspects of a liver transplantation for Budd-Chiari have sometimes differed from transplantation for other diseases. Dense adhesions around the suprahepatic IVC often make a retrograde hepatic dissection the safest method and have allowed the dissection to be done without extension of the operation into the chest in all patients. The development of veno-venous bypass in 1983 had a major impact in this subgroup of transplant patients due to the severe portal hypertension that is usually found with Budd-Chiari. For this reason the veno-venous bypass is usually instituted before the liver dissection is undertaken.

Recurrence of the Budd-Chiari syndrome was seen in two resected liver allografts examined 2.8 and 1.2 years after transplant. Both of these patients had at least one documented period of subtherapeutic anticoagulant treatment. One other allograft in a patient adequately anticoagulated was examined after 1.5 years and had no evidence of Budd-Chiari recurrence. In patient 93 the biopsy at 12 years showed no sign of Budd-Chiari recurrence despite no anticoagulant treatment. It is not possible to know if recurrent Budd-Chiari would have been prevented in those patients who developed recurrence if they had been anticoagulated adequately at all times or if the underlying disease would have caused the problem anyway. It is clear that anticoagulant treatment was essential in some of the patients based on the experience of thrombotic episodes occurring with anticoagulant withdrawal, as well as with reported thrombotic episodes without anticoagulation therapy that did not recur with anticoagulation. If the Budd-Chiari syndrome is caused by anti-thrombin-III or protein C deficiency or by another protein made in the liver, then liver transplantation may be curative in this group of patients and they may not require postoperative anticoagulation. A patient with homozygous protein C deficiency who was cured with liver transplantation has been reported from Pittsburgh.[27]

However, until a subgroup is well defined that does not require anticoagulation, all post-transplant Budd-Chiari patients should be therapeutically anticoagulated. We experienced no anticoagulant complications with close follow-up of all patients. Based on the Cambridge experience in which only 1 of 16 anticoagulated patients had a late thrombotic-related death and in our experience in which 3 of 23 patients had recurrent Budd-Chiari syndrome, at least one of which was not adequately anticoagulated, it certainly seems that liver transplantation is indicated for the Budd-Chiari syndrome when associated end-stage liver disease is present. The underlying disease should be treated as much as is possible.

In summary 23 patients in our experience who had liver transplantation for the Budd-Chiari syndrome were reviewed. Orthotopic liver transplantation for the Budd-Chiari syndrome can be done with acceptable morbidity and mortality rates that seem to be improving. In patients with end-stage liver disease and Budd-Chiari it is the treatment of choice. Further long-term follow-up of patients with shunt surgery for Budd-Chiari, as well as with transplantation for Budd-Chiari, will be needed to determine the best treatment for patients with the Budd-Chiari syndrome and intermediate degrees of liver failure.

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Increased Morbidity in Surgical Patients Undergoing Secondary (Incidental) Cholecystectomy

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Using computerized hospital discharge abstracts for all Vermont residents hospitalized during 1983 and 1984, we examined the question of whether increased morbidity occurs in patients undergoing secondary (incidental) cholecystectomy. Among a cohort of 4183 patients undergoing a primary surgical procedure in which secondary cholecystectomy might have been considered, 69 patients had a secondary cholecystectomy. The surgical wound infection rate was 8.7% in the secondary cholecystectomy group compared to 2.4% in the rest of the cohort (relative risk, 3.7, 95% C.I. 1.7, 8.1). Other postoperative complications occurred in 10.1% of those undergoing secondary cholecystectomy compared to 4.1% in those who did not (relative risk, 2.5, 95% C.I. 1.2, 5.1). The adjusted relative risk for wound infection was 3.3 (95% C.I. 1.4,8.0) and for other surgical complications was 1.7 (95% C.I. 0.8, 3.8). Postoperative length of hospital stay was longer for the secondary cholecystectomy group (mean, 13.8 days) than in the comparison group (mean 8.9 days, p = 0.001). These data suggest that patients undergoing a secondary cholecystectomy may have an increased risk of surgical wound infection and possibly other surgical complications.

ABDOMINAL EXPLORATION IS an integral part of any intra-abdominal surgical procedure. Gallstones are commonly found at this time; the overall prevalence of gallstones in the general population has been estimated at about 20% in one large autopsy study.[1] If gallstones are found during surgical exploration, should the gallbladder be removed? If the benefits of removing the gallbladder outweigh the risks of this additional procedure, the answer should be yes. However, if the risk of performing a secondary (incidental) cholecystectomy is greater than the risk of future morbidity from gallstones left in place, then the answer is no.

Several previous studies have reported no significant increase in morbidity from secondary cholecystectomy.[2-8] However not all studies used appropriate comparison groups to determine the risk of secondary cholecystectomy. For example Kovalcik and coworkers[2] retrospectively examined complication rates after secondary cholecystectomy compared to those after primary cholecystectomy. Other studies have compared the morbidity after secondary cholecystectomy to historical surgical morbidity rates,[3] while still others have not used an explicit comparison group.[4-8]

To address the question of the risks of secondary cholecystectomy relative to an appropriate comparison group, we undertook a retrospective cohort analysis of hospitalized Vermont residents.

Methods

Computerized hospital discharge abstracts for the state of Vermont are available at the Vermont State Health Department. At the time of patient discharge, all hospital medical records are abstracted according to the Uniform Hospital Discharges Data Set (UHDDS) format by hospital employee-coders at each of the 16 nonfederal hospitals in Vermont. Abstracted data are edited for completeness and internal consistency by the Commission on Physician and Hospital Activities (CPHA). The Vermont Department of Health receives an annual computer tape for all discharges from Vermont hospitals. Abstracts of Vermont resident discharges from the Dartmouth-Hitchcock Medical Center (DHMC), the major provider of medical care to Vermont residents outside the state, are received directly from DHMC. Attributes in the data files include age, sex, admitting diagnosis, five discharge codes

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(ICD9-CM),[9] five procedure codes (ICD9-CM), procedure day, length of stay, and hospital charges.

We chose to study all Vermont residents hospitalized in 1983 and 1984 who underwent a primary intra-abdominal surgical procedure in which a secondary cholecystectomy would have been possible to perform based on our knowledge of standard surgical practice. The patients chosen were all those with the first surgical procedure in the discharge abstract data file coded between ICD9-CM 43.5 and 54.5, representing surgical procedures involving any of the digestive organs from the stomach to rectum (Table 1). Also included were patients having retroperitoneal, gynecologic, and arterial surgical procedures done through an abdominal incision in which adequate exposure of the gallbladder could be obtained. We excluded patients whose surgical procedure was endoscopy, percutaneous biopsy, or radiography, or involving a grossly infected surgical field, removal or use of the gallbladder as part of the primary procedure, or common duct exploration. Patients undergoing primary appendectomy were also excluded because the usual surgical incision does not permit easy access to the gallbladder.

TABLE 1. *Surgical Procedures Composing the Vermont Surgical Cohort, ICD9-CM Surgical Procedure Codes, 1983–1984*

Description	ICD9-CM Procedure Code
Inclusions	
Procedures involving the digestive organs from stomach to rectum	43.5–54.5
Bilateral adrenalectomy	07.22
Nephrectomy	55.5–55.55
Abdominal aortic procedures	38.04 38.34, 38.36, 38.64
Total abdominal hysterectomy	68.4
Exclusions	
Primary cholecystectomy	51.22
Primary appendectomy	47.0
Common bile duct explorations/repair	51.36–51.96
Procedures with a Grossly Infected Field	
Incision and drainage abdominal wall	54.0
Drainage intra-abdominal abscess	54.19
Debridement abdominal wall	54.3
Pancreatic drainage	52.01, 52.4
Drainage appendiceal abscess	47.2
Suturing of perforated peptic ulcers	44.4
Endoscopic and Percutaneous Procedures	
Gastroscopy, small intestinal endoscopy	45.12, 45.13
Local excision stomach, duodenum	45.31
Percutaneous liver biopsy	50.11, 50.12
Percutaneous stone extraction	51.96
Primary Procedures Involving Removal or Use of Gallbladder	
Radical pancreaticoduodenectomy	51.27
Anastomosis to intestine or stomach	51.32, 51.34

Primary procedures were grouped in the following categories: retroperitoneal (kidneys or adrenal gland), solid organs (spleen, pancreas, or liver), upper gastrointestinal (abdominal esophagus, stomach, duodenum, or small bowel), lower gastrointestinal (colon or rectum), reproductive organs (abdominal hysterectomy), and others (vascular or abdominal wall).

A secondary cholecystectomy was defined as a patient who had a cholecystectomy (ICD9-CM 51.22) listed as the second through fifth surgical procedure in the discharge abstracts who had a primary surgical procedure, as defined above, performed on the same hospital day. In addition the patient's admitting and primary discharge diagnosis codes were not related to gallbladder or biliary disease.

Morbidity was measured in two categories as follows: (1) postoperative wound infection (ICD9-CM diagnosis code 998.5), and (2) other postoperative complications including cardiac (ICD9-CM 997.1), respiratory (ICD9-CM 997.3), gastrointestinal (ICD9-CM 997.4), and urinary complications (ICD9-CM 997.5). Coexisting adult-onset diabetes mellitus (ICD9-CM 250-250.9) and malignant neoplasms (ICD9-CM 140-209.9), medical conditions that might affect surgical outcome, were included in the multivariate analysis.

Length of postoperative hospital stay was obtained by subtracting procedure day from total hospital stay.

In the univariate analysis, relative risks were calculated with 95% confidence intervals.[10] In the multivariate analysis we used a stepwise logistic regression model to determine the effects of age as a continuous variable, sex, coexisting diabetes, or malignant neoplasm, and primary procedure category on the relative risk of complications due to secondary cholecystectomy using the BMDPLR computer program (BMDP Statistical Systems Inc., Los Angeles, CA).[11] Only variables found to significantly alter the relative risk estimates were included in the calculation of the adjusted relative risk.

Results

A total of 4183 Vermont residents met the criteria for inclusion into the surgical cohort. Of these 69 patients had a secondary cholecystectomy, a rate of 16.5 per 1000 surgical procedures. Table 2 compares the demographic and medical characteristics of the members of the surgical cohort with and without secondary cholecystectomy. The groups differ with respect to age: the secondary cholecystectomy group was an average of 10 years older; 58% were mor than 60 years old, compared to 40% older than 60 years in the no secondary cholecystectomy group. The secondary cholecystectomy group had a higher proportion of patients with a coexisting malignancy. Upper gastrointestinal and reproductive tract operations were more common primary surgical procedures in this group.

TABLE 2. *Characteristics of the Vermont Surgical Cohort: Groups with and Without Secondary Cholecystectomy, 1983–1984*

Characteristics	Total	No Secondary Cholecystectomy (No. of Patients; %)	Secondary Cholecystectomy (No. of Patients; %)
Total patients	4183	4114	69
Male	1346	1324 (32%)	22 (32%)
Female	2837	2790 (68%)	47 (68%)
Age (years)			
Mean (SD)		52.3 (19.4)	62.5 (16.9)
Median age		53	65
Range		1–99	23–86
Coexisting Medical Conditions			
Diabetes mellitus		149 (4%)	5 (7%)
Malignancy		918 (22%)	27 (39%)
Procedure Category			
Retroperitoneal		114 (3%)	2 (3%)
Solid organs		150 (4%)	4 (6%)
Upper GI		393 (10%)	17 (25%)
Lower GI		1431 (35%)	31 (45%)
Reproductive organs		1360 (32%)	4 (6%)
Other		666 (16%)	11 (16%)

Table 3 shows the unadjusted relative risks of wound infection and other surgical complications in the secondary cholecystectomy group. Wound infections occurred in 6 (8.7%) of the 69 patients undergoing secondary cholecystectomy group compared to 97 (2.4%) of the 4114 patients in the rest of the surgical cohort, a relative risk of 3.7 (95% C.I. 1.7, 8.1; p = 0.007). Other surgical complications occurred in 7 (10.1%) of the secondary cholecystectomy patients compared to 168 (4.1%) of the comparison patients, a relative risk of 2.5 (95% C.I. 1.2,5.1; p = 0.02).

In the stepwise logistic regression analysis, only differences in the categories of primary surgical procedure had a significant effect on the risk of surgical wound infection. The adjusted relative risk of wound infection in secondary cholecystectomy patients infection was 3.3 (95% C.I. 1.4, 8.0). Age, coexisting malignancy, and primary procedure category significantly affected the risk of other complications. The adjusted relative risk estimate for other complications was 1.7 (95% C.I. 0.8, 3.8).

The mean length of postoperative hospital stay was 13.8 days in the secondary cholecystectomy group compared to 8.9 days in the comparison group (p = 0.001, unpaired, two-tailed t test).

Discussion

Our data suggest that among hospitalized Vermont residents undergoing a surgical procedure in which direct examination of the gallbladder was possible, those patients having a secondary cholecystectomy had elevated rates of both postoperative wound infection and other surgical complications compared to those not having the additional procedure. The elevated risk of secondary cholecystectomy persisted after controlling for factors that might influence surgical complication rates such as differences in primary procedure category, age, and coexisting medical diagnoses.

These findings are plausible; it is not unexpected that two surgical procedures would have a greater risk of complications than one. A second procedure extends the duration of the operation, may require a longer incision, and involves additional manipulation of abdominal contents. In the case of cholecystectomy, contamination of the surgical site with bile, which may harbor micro-organisms, may occur. These factors are expected to increase complication rates.

Several other authors have not found the risks of secondary cholecystectomy to be excessive. Kovalcik and coworkers[2] found a wound infection rate of 3.7% and an overall complication rate of 20% among 54 patients having

TABLE 3. *Surgical Complications in the Vermont Surgical Cohort, 1983–1984*

	No Secondary Cholecystectomy (No. of Patients; %)	Secondary Cholecystectomy (No. of Patients; %)	Unadjusted Relative Risk
Total			
Wound infections	97 (2.4%)	6 (8.7%)	3.7
Other complications	168 (4.1%)	7 (10.1%)	2.5
Male Patients			
Wound infections	30 (2.3%)	2 (9.1%)	4.0
Other complications	71 (5.4%)	1 (4.5%)	0.9
Female Patients			
Wound infections	67 (2.4%)	4 (8.5%)	3.5
Other complications	111 (4.0%)	6 (12.8%)	3.2
Procedure Type			
Retroperitoneal wound infections	3 (2.6%)	0 (0%)	0
Other complications	8 (7.0%)	0 (0%)	0
Solid Organs			
Wound infection	4 (2.7%)	2 (50.0%)	18.8
Other complications	6 (4.0%)	1 (25.0%)	6.7
Upper G.I.			
Wound infection	16 (4.1%)	3 (17.6%)	4.3
Other complications	35 (8.9%)	2 (11.8%)	1.3
Lower G.I.			
Wound infection	40 (2.8%)	0 (0%)	0
Other complications	66 (4.6%)	3 (9.7%)	2.1
Reproductive Tract			
Wound infection	29 (2.1%)	0 (0%)	0
Other complications	32 (2.4%)	0 (0%)	0
Other Procedures			
Wound infection	5 (0.8%)	1 (9.1%)	12.1
Other complications	21 (3.2%)	1 (9.1%)	2.9

a secondary cholecystectomy compared to rates of 1.6% and 14%, respectively, for 1148 patients having a primary cholecystectomy only. Despite odds ratios of approximately 2.4 for wound infection and 1.6 for other complications, their results did not achieve statistical significance and were not viewed by the authors as indicating an excess risk of secondary cholecystectomy. Pratt and coworkers[3] found no excess risk of complications among 95 patients undergoing hysterectomy and cholecystectomy compared with historical rates. Several other reports of case series of secondary cholecystectomy patients have found complication rates deemed not to be in excess of usual surgical practice,[4–8] although some authors caution that the additional procedure should only be done in selected, stable patients.

The strengths of our study include its design, which identifies a cohort of surgical patients containing a high proportion of the Vermont population undergoing surgical procedures in which a secondary cholecystectomy might be performed. This helps to avoid the potential referral biases and lack of representativeness of the study population due to patient recruitment patterns and local surgical practices that may occur when a case series is assembled at a single medical institution. The comparison population in this study is the population from which secondary cholecystectomy patients are drawn. Complication rates are compared to those accompanying the underlying surgical procedures in that population rather than historical controls or primary procedures. This is important because comparing the complication rates of secondary cholecystectomy to those in cholecystectomy alone[2] may underestimate the risk of secondary cholecystectomy: primary cholecystectomy is often performed for an indication such as biliary colic or acute cholecystitis in which higher rates of infection and complications might be expected. Using historical surgical complication rates as a comparison may[3] also overestimate the baseline risk because surgical complication rates may have improved since the historical data were collected.

Our data agree with overall wound infection rates published by several other large prospective studies of wound infection rates.[12–14] We found the highest wound infection rates in upper gastrointestinal procedures, which is also comparable to the experience of others.[15]

There are several potential caveats in interpreting the results of our study. First we rely on a secondary data source that was collected for other purposes and lacks more detailed information about factors that may influence the outcome in individual patients, such as a more accurate assessment of medical condition, use of prophylactic antibiotics, actual duration of surgery, and so on. It is unlikely, however, that patients undergoing secondary cholecystectomy in our study were in such poor medical condition that would explain a poorer outcome than in members of the surgical cohort in general. In addition we adjust for the factors probably related to severity of medical condition and found that secondary cholecystectomy still conferred a higher risk of complications.

Second we cannot be sure that the secondary cholecystectomies were not actually coprimary procedures performed for a pressing medical indication, for instance, symptomatic gallstones, rather than for purely prophylactic reasons. The balancing of risks and benefits of secondary cholecystectomy in such patients would lean more heavily toward surgery and so it would not be fair to include them in the present analysis. We tried to exclude patients with a clear indication for secondary cholecystectomy by excluding from the analysis those with biliary or gallbladder disease listed as the admitting or primary discharge diagnosis.

In weighing the risks and benefits of secondary cholecystectomy, much emphasis has been placed in the medical literature on the question of the natural history of silent gallstones. Several studies of cohorts of persons identified as having gallstones have found that biliary symptoms eventually develop in up to 50%.[16–18] However a more recent study of 123 persons with gallstones detected by routine cholecystographic screening of an otherwise healthy population estimated that only 18% would eventually develop symptoms.[19] In this paper we try to address the other side of the equation. Our data suggest that the risk of secondary cholecystectomy also needs to be taken into account when considering whether to perform this procedure. Clearly not all patients with gallstones will experience morbidity in the future, whereas those undergoing secondary cholecystectomy may experience an immediate increased risk of morbidity. Our results suggest that further studies of the risks of secondary cholecystectomy using primary data sources should be performed to determine in which patients the risk is warranted or if the magnitude of the risk is sufficient to recommend discontinuing secondary cholecystectomy as a routine surgical procedure.

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Emergency Surgery for Severe Acute Cholangitis

The High-Risk Patients

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Emergency surgery for patients with severe acute cholangitis carries formidable postoperative morbidity and mortality rates. A retrospective study was conducted on 86 consecutive patients who had exploration for the calculous obstructions to identify the high-risk population to guide better management. Septicemic shock was present in 55 patients before surgery. All patients had ductal exploration under general anesthesia. Additional procedures included cholecystectomy (n = 55), cholecystostomy (n = 5), and transhepatic intubation (n = 2). Complications and deaths occurred in 43 (50%) and 17 (20%) patients, respectively. Multivariate analysis on the 25 clinical (n = 14) and biochemical (n = 11) parameters evaluated yield the following five predictive factors (relative risk): the presence of concomitant medical problems (4.5); pH less than 7.4 (3.5); total bilirubin more than 90 μmol/l (3.1); platelet less than 150 × 10^9/l (2.9), and serum albumin less than 30 g/L (2.9). In the presence of three or more risk factors, postoperative morbidity and mortality rates were 91% and 55%, respectively, which were significantly higher than those with two or less risk factors (34% and 6%, respectively). As thrombocytopenia developed even with transient hypotension, timely ductal decompression would improve outcome of these patients after surgery. For the high-risk population, application of nonoperative biliary drainage might be considered.

INITIAL MANAGEMENT OF patients with acute cholangitis should be conservative with appropriate antibiotics because the majority of them would resolve.[1] When sepsis progresses despite vigorous supportive measures, biliary decompression becomes mandatory. Under such circumstances emergency surgical drainage carries formidable morbidity and mortality risks. The present analysis of our experience with emergency surgery for patients with acute cholangitis was conducted to identify the high-risk population for postoperative problems to guide better management.

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Patients and Methods

The clinical records of all patients who had acute cholangitis secondary to choledocholithiasis managed at the Department of Surgery, University of Hong Kong at Queen Mary Hospital were reviewed. The diagnosis of cholangitis attack was based on the presence of hyperbilirubinemia with either fever or abdominal pain. Patients whose biliary obstruction was secondary to either primary or metastatic malignant disease were excluded. Severe acute cholangitis (SAC) was considered when progression of biliary sepsis was evident, despite an adequate trial of conservative treatments. Between January 1984 and September 1988, 86 consecutive patients with SAC who had emergency surgery for biliary decompression were included in the present retrospective study. There were 41 men and 45 women with age range from 28 to 97 years (mean, 67 ± 14 years).

Hospital mortality was defined as death within the same hospitalization after emergency biliary tract operation regardless of its cause. Death within 48 hours after surgery was attributed to biliary sepsis when other obvious contributory causes are absent. Because patients included were often critically ill, ductal exploration might be limited to choledochotomy and T-tube insertion. The presence of residual stones was not regarded as a postoperative morbidity. The diagnosis of renal failure was made when postoperative serum creatinine doubled or exceeded 0.18 μmol/L among patients with normal preoperative values (serum creatinine ≤ 0.13 μmol/L); or a rise of 0.10 μmol/L over its deranged preoperative value.[3] Necessity for mechanical ventilation as judged clinically at any time after surgery is considered respiratory failure.

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The following 25 preoperative clinical and laboratory data were evaluated for the risk of postoperative death: maximum temperature recorded; duration of fever (temperature ≥ 37.5 C); systolic blood pressure (the lowest value recorded before surgery and at induction of anesthesia); duration of preoperative hypotension (systolic blood pressure ≤ 100 mmHg) when present and results of resuscitation; timing of surgery with respect to admission; history of previous biliary tract surgery; complete blood picture (hemoglobin, white cell and platelet counts); liver function tests (total bilirubin, alkaline phosphatase, gamma glutyl-transpeptidase, alanine transaminase, and aspartate transaminase); and renal function tests (serum urea and creatinine, and the worst arterial blood gas result sampled within 24 hours before exploration). Concomitant medical problems (CMP), which included underlying nonbiliary tract malignancies, were assumed to be of equal weight for analysis without consideration of their individual degrees of severity (Table 1). Operative findings included location of the calculi and/or benign stricture; diameter and tension of the common bile duct noted at surgery and suppuration of the aspirated common duct bile were also studied.

Statistical analyses were conducted with standard computer programs. Chi square test with Yates' correction, Student's t test were used when appropriate. Logarithmic transformation was used among continuous variables with skewed distribution. Multivariate analysis was conducted with linear discriminant analysis. Statistical significance was taken when probability was less than 0.05.

Results

Clinical Features

Features of the Charcot's triad, fever (maximal temperature ≥ 38.3 C), jaundice (total bilirubin ≥ 26 mmol/L), and abdominal pain, were the most frequent presentations that were positive in 66%, 93%, and 90% of patients, respectively. Presence of all three features was noted in 48 (56%) patients. Septicemic shock was present in 55 (64%) of these 86 patients before surgery. While 34 patients had hypotension at presentation or within the initial 24 hours after admission, 17 of the remaining 21 patients developed fulminant sepsis within the first 24 to 72 hours. Despite active resuscitation, 30 of the 55 patients were hypotensive at the time of induction of anesthesia. One patient who was normotensive had shock immediately before surgery. Among the 30 patients with associated medical problems, five of them had two or more diseases (Table 1). History of previous biliary tract surgery was present in 24 patients, 20 of whom had prior cholecystectomy. All of the remaining four patients had another ductal exploration before the episode was evaluated.

TABLE 1. *Concurrent Medical Problems Among Patients with Severe Acute Cholangitis*

Problems	No. of Patients
Myocardial ischemia	12
Renal dysfunction	12
Cirrhosis	5
Malignancy	4
Diabetes mellitus	3
Bronchopneumonia	1

Operative Findings and Procedures

Emergency surgery was conducted within the first 24 hours after presentation in 42 (49%) patients. Among the remaining 44 patients, 10 (12%) patients were explored after 72 hours of observation. None of the patients included had any attempt for nonoperative biliary drainage.

All emergency operations were performed under general anesthesia. Among 74 (86%) of the 86 patients with dilated common duct (ductal diameter larger than 10 mm), 62 of them were under tension. Bile aspirated from common bile duct was considered purulent in 32 (39%), turbid in 38 (46.3%), and clear in 12 of the 82 patients. Intrahepatic calculi, with (n = 12) or without (n = 6) associated ductal strictures, was encountered in 18 of the 84 patients with complete clinical and radiographic documentation of their biliary tract pathology. None of the above-mentioned operative findings related to either the presence of preoperative hypotension or postoperative mortality.

Extent of CBD exploration depends on the patient's hemodynamic status at surgery. Intraoperative choledochoscopy and T-tube cholangiogram were not routinely performed. Ductal exploration alone was conducted in 24 patients. Additional procedures included cholecystectomy (n = 55), cholecystostomy (n = 5), and transhepatic intubation (n = 2).

Bacteriology

Blood culture was positive among 43 (74%) of 58 patients with sample collected. *Escherichia coli* was the most common isolated bacteria (41%), followed by mixed growth and *Klebsiella*. Bile culture of the 56 patients had a similar pattern. Successful isolation of pathogens was obtained in 50 (89.3%) patients, with *Escherichia coli* as the most common organism (37.5%). Identical pathogens were isolated from both bile and blood samples in 20 of 61 patients. Details of the bacteriology results are shown in Table 2.

Operative Morbidity and Mortality

Postoperative morbidities occurred in one half of the patients studied (Table 3). More than one complication

TABLE 2. *Microbiology*

Organisms Isolated	Source of Culture	
	Bile	Blood
Escherichia coli	34	35
Klebsiella *var.*	15	10
Bacteriodes *fragilis*	5	1
Edwardsiella *tarda*	2	2
Streptococcus fecalis	2	6
Other	9	4
Single	33	36
Mixed	17	7
No growth	6	15

was noted in 17 patients. In the presence of complications, which included cardiac ($p < 0.001$), pulmonary ($p < 0.001$), and renal ($p < 0.05$) decompensation, there was a significant increase in mortality. Twenty-three patients (27%) had residual stones. Except for three patients who died soon after surgery, all of the remaining 20 patients had successful ductal clearance with postoperative flexible choledochoscopy. Seventeen (20%) patients died from various causes (Table 4).

Risk Factors

Univariate analysis revealed ten variables that significantly correlated with hospital mortality rates for patients with SAC after surgery (Table 5). The presence of persistent hypotension despite fluid resuscitation and inotropic support did not affect the outcome of these patients. Using multivariate analysis five variables were found to be of independent predictive value (relative risk) as listed in Table 6: the presence of concomitant medical problems (4.5%); pH less than 7.40 (3.5%); Log_{10}(total bilirubin) less than 90 mmol/L (3.1%); platelet count less than 150 $\times 10^9$ (2.9%); and serum albumin less than 30 g/L (2.9%). The discriminant equation is

TABLE 3. *Postoperative Morbidities for Patients with Severe Acute Cholangitis*

Complications	No. of Patients
Renal failure	17
Respiratory failure	13
Cardiac arrhythmia	11
Wound infection	8
Bronchopneumonia	4
Heart failure	3
Gastrointestinal bleeding	3
Myocardial ischemia	2
Wound dehiscence	2
Pleural effusion	1
Renal abscess	1
Disseminated coagulopathy	1

TABLE 4. *Causes of Death for Patients with Acute Cholangitis After Emergency Surgery*

Causes of Death	No. of Patients
Heart failure	2
Bronchopneumonia	1
Multiorgan failure	8
Fulminant sepsis	6
Total	17

$$R = 0.27(\text{Platelet}) \times 10^{-2} + 0.51(\text{Albumin}) \times 10^{-1} - 1.3(\text{CMP}) - 0.72(\text{Log}_{10}\text{bilirubin}) + 9.2(\text{pH}) - 69$$

where R is the function producing the best separation between patients who survived (mean value, 0.43) and those who succumbed (mean value, −1.7) after surgery for their SAC. The sensitivity, specificity, and percentage of cases correctly classified were 73%, 93%, and 89%, respectively.

Deaths observed increased with the number of risk factors present when they were assumed to be of equal weight –0(0%), 1(3%), 2(7.1%), 3(36.4%), 4(83.3%), and 5(100%). Extrapolation of these data for the prediction of postoperative morbidities provides a satisfactory correlation –0(0%), 1(32%), 2(48%), 3(82%), 4, and above (100%). Among the high-risk patients with three or more of the above risk factors, postoperative morbidity and mortality rates were 91% and 55%, respectively, which were significantly higher than those with two or less risk factors (34% and 6%, respectively; $p < 0.001$).

Among different clinical parameters evaluated, development of thrombocytopenia (platelet count less than 150 $\times 10^9$) correlated significantly with the lowest systolic

TABLE 5. *Factors Associated with Postoperative Mortality in Patients with Severe Acute Cholangitis*

Factors	Survival (n = 69)	Died (n = 17)	Probability
Age (yrs)	64 ± 14	73 ± 10	0.02
Platelet ($\times 10^9$/mL)	176 ± 108	98 ± 73	0.01
Urea (mmol/L)	9 ± 10	18 ± 9	0.002
Creatinine (mmol/L)	0.13 ± 0.08	0.23 ± 0.13	0.0001
Albumin (g/L)	36 ± 7.7	31 ± 8.9	0.015
Total bilirubin (μmol/L)	71 ± 2.3	115 ± 1.6	0.03
Duration of fever (hrs)*	6.8 ± 22	1.1 ± 31	0.04
Duration of hypotension (hrs)*	0.02 ± 22	1.24 ± 12	0.03
Percentage of patients with CMP†	26	71	0.002
Percentage of patients with pH <7.40†	17	53	0.006

Values represented mean ± standard deviation.
Statistical analysis with two-tailed Student's t test unless specified.
* Logrithmic transformation.
† Statistical analysis by chi square test with Yates' correction.

TABLE 6. *Selected Predictive Factors for Postoperative Mortality for Patients with Severe Acute Cholangitis*

Factors	Percentage of Patients Who Died	Probability
pH		
<7.40	43	0.006
≥7.40	12	
Platelet count (10^9/mL)		
<150	29	0.05
≥150	10	
Serum albumin (gm/L)		
<30	38	0.02
≥30	13	
Concomitant medical problems		
Present	40	0.002
Absent	9	
Total bilirubin (μmol/L)		
≥90	31	0.02
<90	9	

blood pressure recorded within 24 hours before surgery ($p < 0.001$) and duration of hypotension of one hour or less ($p < 0.001$).

Discussion

It is well recognized that acute cholangitis has a wide spectrum of clinical presentations. With adequate antibiotics and fluid therapy, decisions for therapeutic intervention rest solely on the progression of disease regardless of the degree of biliary suppuration inside the obstructed ductal system. Hence SAC was used in the present report to describe the clinical settings in which emergency biliary drainage is considered necessary as a life-saving measure.

Results of emergency surgery for calculous cholangitis were disappointing. When patients with malignant biliary obstruction were included, postoperative mortalities, which ranged from 21.6% to 40%, have been reported even among recent series.[2,4–6] Few attempts have been made in the past to identify the high-risk population among patients with severe calculous cholangitis. Scattered information obtained from literatures was based on patients who had either different etiologies for their biliary obstruction,[4,5,7] urgency of biliary decompression,[4,5] and means of biliary drainage.[5] In contrast to these previous reports, the current evaluation focused on a specific population of patients who all had emergency surgery for their SAC secondary to choledocholithiasis.

Reduction of those potentially reversible risk factors identified from the current study would probably improve survival rates. Timely intervention remains the essence for the successful management of patients with SAC.[8] Even in the presence of transient hypotension, the chance of developing thrombocytopenia was significantly increased. With clinical signs of deterioration, urgent relief of ductal obstruction should be performed to avoid progression to septicemic shock. Early aggressive ductal drainage is indicated even among patients with persistent hypotension. Postoperative outcomes of the 30 patients who remained in septicemic shock before surgery was similar to outcomes of patients who were successfully resuscitated.

Low serum albumin levels have been shown by different series to adversely affect the outcome of patients, with or without history of cholangitic attacks, undergoing biliary tract surgery.[3,5,9,10] Contribution of concomitant medical illness to the postoperative risk of death for patients with SAC has been controversial. According to O'Connor et al.,[4] associated medical illness has no significant bearing on the postoperative mortality rate among their 65 patients. Results of the present study has validated the risk of having concurrent medical problems, regardless of individual severity, as noted by Leese et al.[5] The presence of acidosis (pH less than 7.4) coincides with none of the clinical and biochemical factors evaluated in the present study. Hence a satisfactory explanation and an appropriate preventive measure could not be offered.

Among patients with benign biliary obstruction, postoperative mortality rates correlated well with the depth of jaundice.[11] Preoperative correction of hyperbilirubinemia might improve outcome of these patients with severe cholangitic attacks. While surgery has been the conventional means for emergency biliary drainage, recent results with the use of nonoperative measures have been good. Percutaneous biliary drainage could be established with transhepatic catheters.[12–14] After endoscopic papillotomy followed by active instrumental stone extraction[5,15,15] or introduction of a nasobiliary catheter,[17] decompression of the obstructed biliary system has been reported among patients with calculous disease. When successful, resolution of sepsis was observed within 24 hours with amelioration of jaundice during the subsequent week with either approach.

In the present study, a high-risk population (three or more risk factors) among patients with fulminant calculous cholangitis undergoing emergency surgery has been identified. Because emergency exploration would significantly increase the number of postoperative deaths when biliary sepsis failed to respond to antibiotic therapy,[7] application of nonoperative measures as an initial intervention could potentially benefit these selected patients. Uncontrolled data have demonstrated that successful conversion of the life-threatening condition to an elective operation has reduced both postoperative morbidity and death with either percutaneous or endoscopic approaches.[5,13,14] Further clinical studies are necessary for the proper evaluation of the role of these nonoperative measures in the management of patients with SAC according to their risk for postoperative death.

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Coelioscopic Cholecystectomy

Preliminary Report of 36 Cases

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Intra-abdominal endoscopy, routinely used for gynecologic operations can be extended safely for cholecystectomy in uncomplicated cholelithiasis. Thirty-six patients underwent coelioscopic cholecystectomy with few and only benign complications. The main advantages are cosmetic preservation, reduction of postoperative pain, shortening of hospital stay, and early recovery of a normal activity.

IN THE LAST DECADE, advances in endoscopic equipment have allowed the development of endoscopic surgical treatment for various gynecologic affections.[1,2] Endoscopic appendicectomy has also been reported and sometimes routinely performed.[3,4] Endoscopic abdominal surgery has been extended safely to free peritoneal adhesions.[1,4] We believe that this procedure could be indicated in usual cholecystectomy for nonacute cholecystis. Many advantages should be expected: cosmetic preservation, rapid disappearance of pain with reduction of the hospitalization time, and the ability to return to work at the end of the hospital stay. Furthermore the risk of wound dehiscence, mostly in cases of obesity, is avoided. We report here our experience.

Patients and Methods

After training on pigs the feasibility and innocuous nature of endoscopic cholecystectomy, we have performed this procedure on 36 patients from May to December 1988. In the same time about 100 patients had classical cholecystectomy through minilaparotomy.[5]

All patients were fully informed of the planned procedure of initial endoscopy and possible subsequent laparotomy and gave consent. There were five men and 31 women. The mean age was 49 years (range, 29 to 86 years). None of them had acute cholecystis. Ten patients had no complaints and 26 did (mainly pain).

The day before the operation an intravenous cholangiogram was performed. It was normal in all patients. None of them had common bile duct calculi, three had cystic stone, and 28 had functional gallbladder.

Technique

All patients were operated on under general anesthesia with endotracheal intubation to allow immediate transition from endoscopic operation to laparotomy. Nasogastric tube was inserted to prevent distension of the stomach before the abdominal wall puncture and to facilitate endoscopic exploration. The patient was positioned horizontally in typical double access position and could be brought into Trendelenburg's or opposite position.

Instruments for endoscopic cholecystectomy are, up to now, the same as those used for gynecologic surgery[2] (some instruments that are more adapted are in preparation): two trocar sheaths with trumpet valves of 10 mm and two trocar sheaths of 5 mm; one monocular endoscope of 10 mm with cold-light optic and video set; a carbon dioxide gas insufflator with monitoring of the abdominal pressure; an insufflating needle; an aquapurator alternating aspiration and insufflation of physiologic saline solution; a set of endoscopic instruments: scissors with coagulation, atraumatic grasping forceps to catch the gallbladder, craw forceps to grasp and extract the gallbladder, coagulating forceps for performing some hemostasis, and a clip applicator with an 8-mm titane clip.

Surgical Procedure (Figs. 1 and 2)

The pneumoperitoneum is created at the preselected pressure of 14 mm Hg through the umbilicus with the

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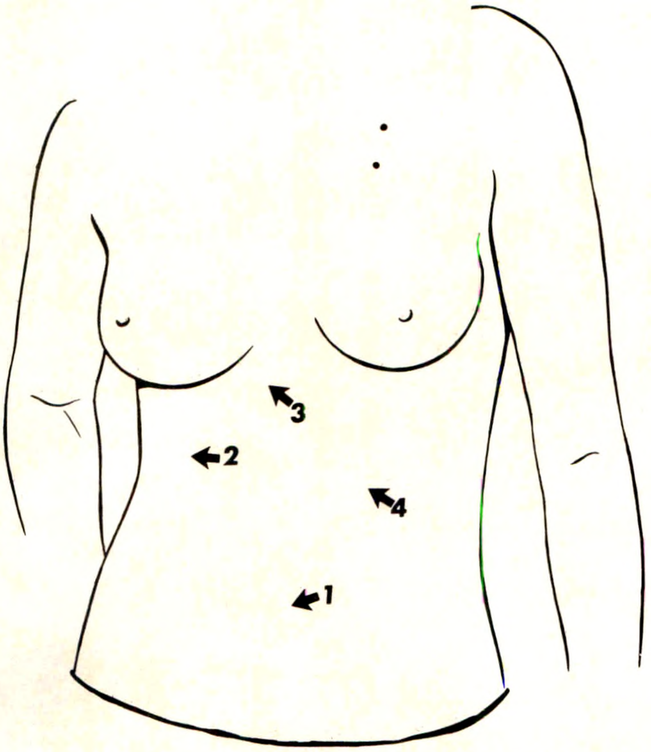

FIG. 1. Abdominal insertion areas: (1) endoscope; (2) atraumatic grasping forceps; (3) aquapurator as a liver retractor; and (4) endocoagulation scissors, clip applicator, and gallbladder forceps extractor.

veress needle. Then the endoscope is inserted through a 10-mm trocar sheath in the upper part of the umbilicus. A circular inspection of the intra-abdominal structures is performed and the gallbladder is inspected. If necessary a needle can be inserted to empty the gallbladder and to perform an x-ray cholangiogram. If the cholecystectomy seems possible, the three others trocar sheaths are inserted. An atraumatic forcep is introduced by puncture with the 5-mm trocar sheath in the subcostal area to catch the gallbladder. A second 5-mm trocar sheath is inserted in an epigastric paramedian point for the aquapurator, which is used also as a liver retractor. The third trocar sheath (10 mm) is inserted in the left upper part of the abdomen. Through it are inserted coagulating scissors or hook for dissection and the clip applicator to control the cystic artery and duct. At the end of the operation the gallbladder is freed (in a retrograde manner) and removed with the craw forceps through the left 10-mm trocar sheat. In cases of big calculi (30 mm or more), this incision must be enlarged on the stone block.

After a final examination within the abdomen for complete hemostasis, the subhepatic area is irrigated, aspirated, and occasionally drained with a small tube. Gas is then released, trocar sheaths are removed, and skin is closed with clips.

Results

Thirty-nine patients had an attempt of endoscopic cholecystectomy. In three patients endoscopic exploration showed pyocholecystis. Therefore we rejected endoscopic operation and these patients underwent minilaparotomy[5] with conventional cholecystectomy.

All others patients underwent endoscopic cholecystectomy. Two complications occurred. One occurred during the procedure and was related to a cystic arterial bleeding due to a tear of a fragilized vessel by clip; a minilaparotomy was immediately performed and bleeding was promptly controlled with easy recovery. The second complication occurred in a 73-year-old woman 48 days after operation. After a simple postoperative course this patient was admitted for abdominal pain. Echography showed subhepatic collection and laparotomy revealed choleperitoneum. There was no leakage from the cystic duct and choleperitoneum was related to the gallbladder bed. It was evacuated and drained with no further complications.

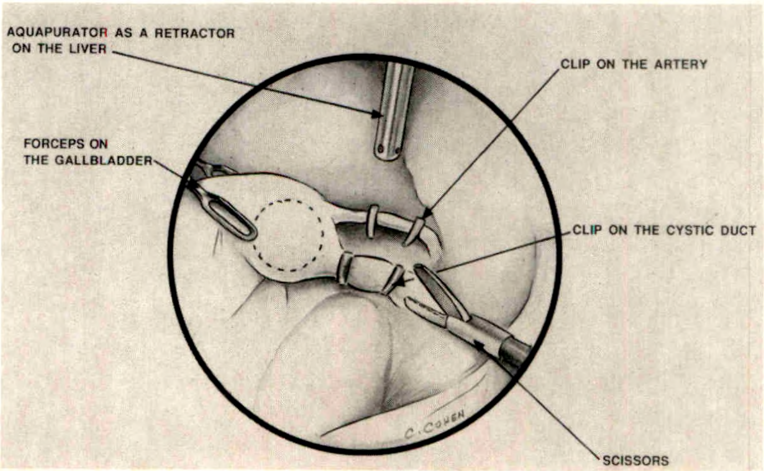
AQUAPURATOR AS A RETRACTOR ON THE LIVER
CLIP ON THE ARTERY
FORCEPS ON THE GALLBLADDER
CLIP ON THE CYSTIC DUCT
SCISSORS
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FIG. 2. Endoscopic aspect of the biliary pedicle.

For the 34 others patients intestinal transit generally recovered within 24 hours. Patients felt some discomfort during the first or the second postoperative day with scapulary pain related to pneumoperitoneum. However all patients were painless within 48 hours. Patients were discharged between the third and seventh postoperative day while recovering completely normal activity.

Discussion

These results demonstrate the feasibility and the safety of endoscopic cholecystectomy for nonacute cholecystis. This procedure must be performed under general anesthesia with tracheal intubation to permit prompt laparotomy when necessary. Cosmetic advantages are evident and are important in young woman. Rupture of parietal incision is avoided. Endoscopic abdominal surgery also reduces postoperative intestinal and and parietal adhesions. Overall this new surgical procedure provides a very simple postoperative course with reduction of pain and rapid recovery of abdominal transit. Our patients were discharged from the hospital between the third and seventh day after operation because of French hospital policy, but all of them could have been discharged earlier. The major advantage of this procedure is probably the rapid recovery of the patient with the complete ability to return to normal activity and/or to work at the end of the hospital stay.

Theoretically previous umbilical laparotomy is a contraindication for this procedure, but endoscopic abdominal surgery can be indicated to correct some abdominal adhesions.[3]

Today our indications are limited to nonacute cholecystis with calculi diameters measuring less than 30 mm. For larger stones an extracorporeal lithotripsy is under experimentation. A perioperative intracorporeal lithotripsy could also be used with this procedure. With more experience and better-adapted instruments, indications may be extended. However this safe and feaisible procedure remains a challenge for surgeons.

Note Added in Proof

Since submission of this article on October 31, 1989, a total of 220 laparoscopic cholecystectomies have been performed with no complications for the last 180 patients.

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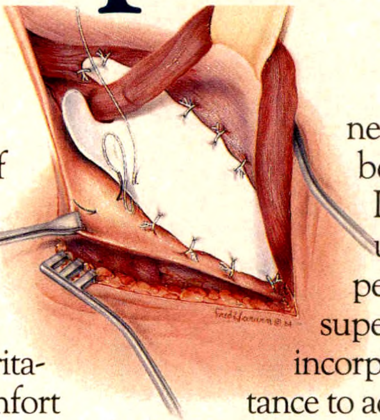

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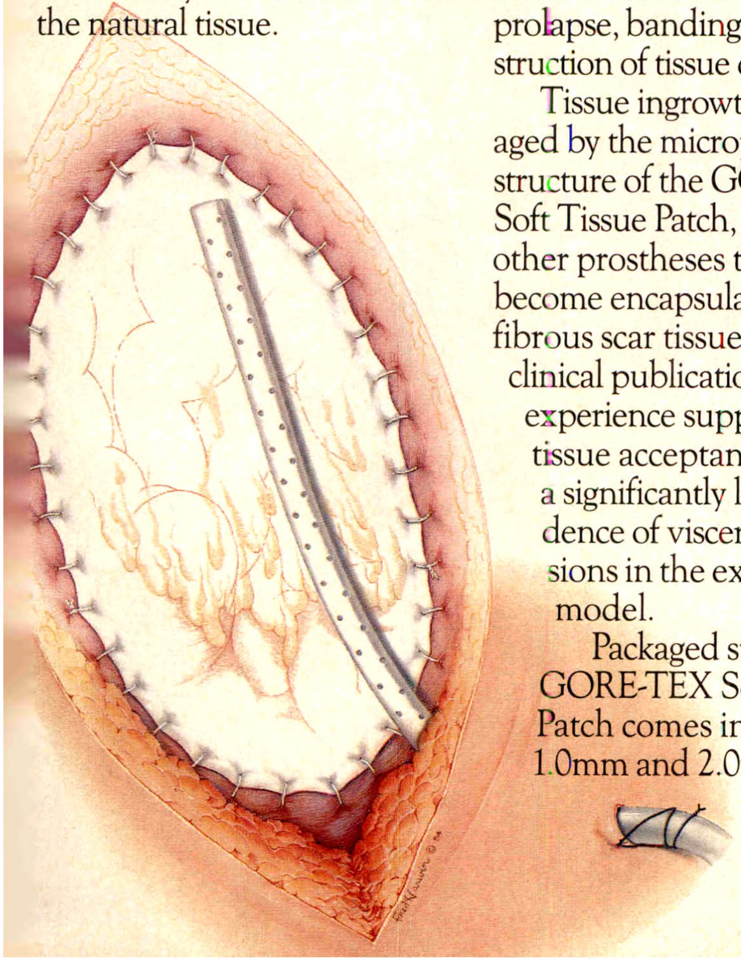

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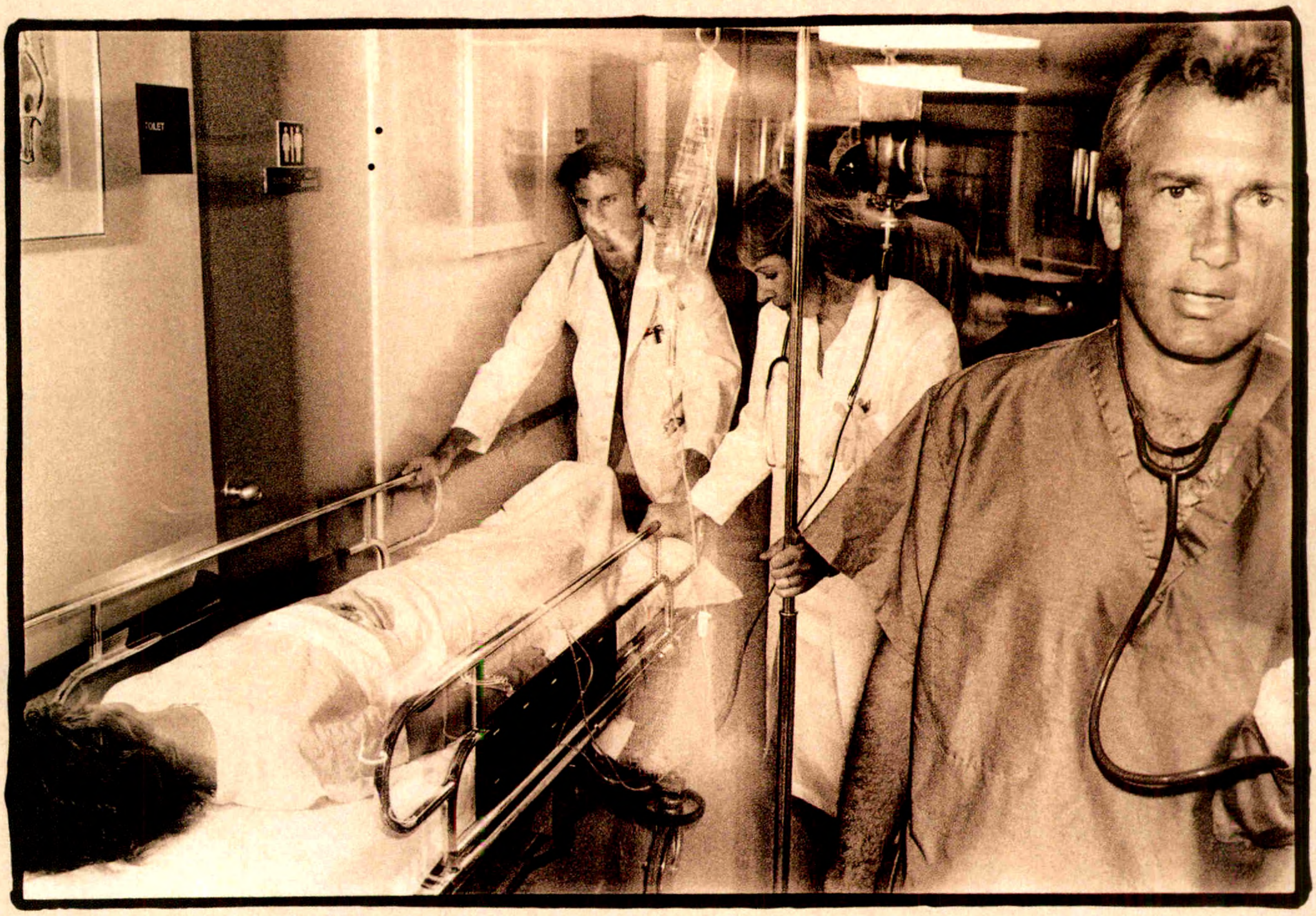

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INDICATIONS AND USAGE
UNASYN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.
Skin and Skin Structure Infections caused by beta-lactamase producing strains of *Staphylococcus aureus, Escherichia coli,* Klebsiella* spp.* (including *K. pneumoniae**), *Proteus mirabilis,* Bacteroides fragilis,* Enterobacter* spp.,* and *Acinetobacter calcoaceticus.**
Intra-Abdominal Infections caused by beta-lactamase producing strains of *Escherichia coli, Klebsiella* spp. (including *K. pneumoniae**), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*
Gynecological Infections caused by beta-lactamase producing strains of *Escherichia coli,** and *Bacteroides* spp.* (including *B. fragilis**).
*Efficacy for this organism in this organ system was studied in fewer than 10 infections.
While UNASYN* (ampicillin sodium/sulbactam sodium) is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.

CONTRAINDICATIONS
The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS
SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.
SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS
General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.
Drug Interactions: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.
Drug/Laboratory Test Interactions: Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with UNASYN.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.
Pregnancy
Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)
Labor and Delivery: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.
Nursing Mothers: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.
Pediatric Use: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.

ADVERSE REACTIONS
UNASYN is generally well tolerated. The following adverse reactions have been reported.
Local Adverse Reactions
Pain at IM injection site—16% Pain at IV injection site—3%
Thrombophlebitis—3%
Systemic Adverse Reactions
The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.
Additional systemic reactions reported in less than 1% of the patients were: itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.
Adverse Laboratory Changes
Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:
Hepatic: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.
Hematologic: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.
Blood Chemistry: Decreased serum albumin and total proteins.
Renal: Increased BUN and creatinine.
Urinalysis: Presence of RBC's and hyaline casts in urine.
The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.
Gastrointestinal: Gastritis, stomatitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.
Hypersensitivity Reactions: Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin (see WARNINGS).
Hematologic: In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

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INDICATIONS AND USAGE

UNASYN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.

Skin and Skin Structure Infections caused by beta-lactamase producing strains of *Staphylococcus aureus*, *Escherichia coli*,* *Klebsiella* spp.* (including *K. pneumoniae**), *Proteus mirabilis*,* *Bacteroides fragilis*,* *Enterobacter* spp.,* and *Acinetobacter calcoaceticus*.*

Intra-Abdominal Infections caused by beta-lactamase producing strains of *Escherichia coli*, *Klebsiella* spp. (including *K. pneumoniae**), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*

Gynecological Infections caused by beta-lactamase producing strains of *Escherichia coli*,* and *Bacteroides* spp.* (including *B. fragilis**).

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

While UNASYN* (ampicillin sodium/sulbactam sodium) is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.

CONTRAINDICATIONS

The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.

Drug/Laboratory Test Interactions: Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with UNASYN.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy

Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)

Labor and Delivery: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.

Pediatric Use: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.

ADVERSE REACTIONS

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Thrombophlebitis—3%

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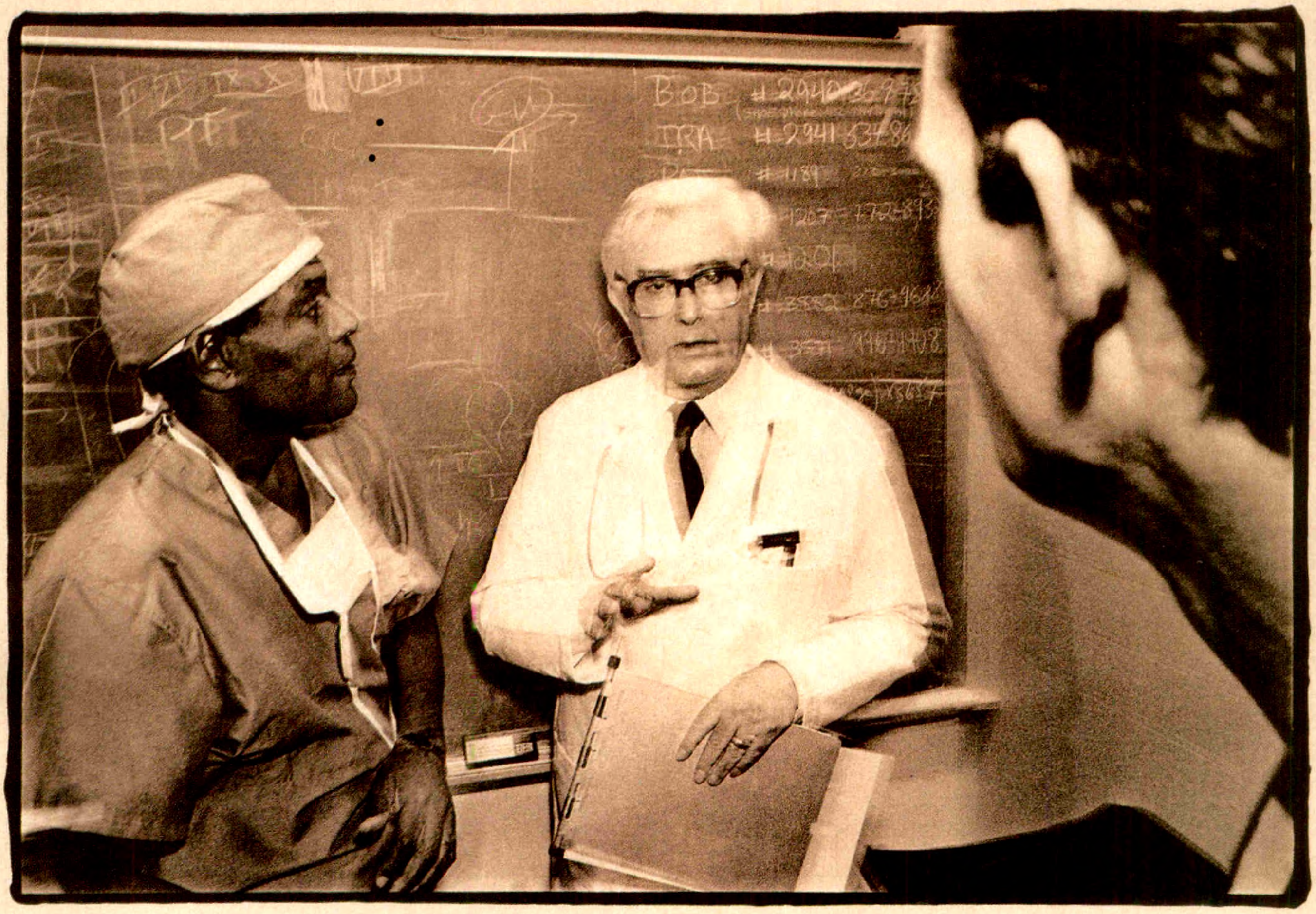

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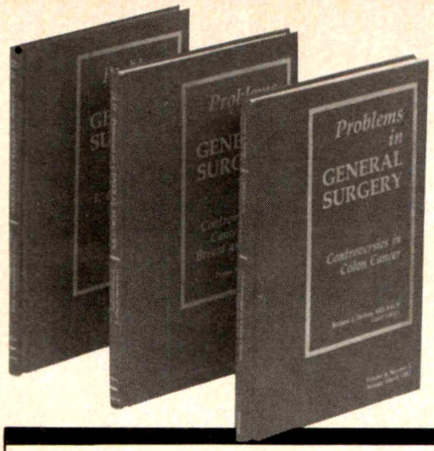

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Benign Smooth Muscle Tumors of the Gastrointestinal Tract

A 24-Year Experience

BRUCE K. MORGAN, M.D.,* CAROLYN COMPTON, M.D., PH.D.,† MICHAEL TALBERT, M.D.,†
WILLIAM J. GALLAGHER, M.D.,* and WILLIAM C. WOOD, M.D.*

From the Departments of Surgery and Pathology,†*
Massachusetts General Hospital Cancer Center, Harvard
Medical School, Boston, Massachusetts

Between 1963 and 1987, 131 patients with benign gastrointestinal stromal tumors, primarily leiomyomas, were treated at the Massachusetts General Hospital. Eighty per cent of tumors were located in stomach or small intestine. Two thirds of the tumors were discovered in symptomatic patients before operation by a variety of diagnostic studies. A mitotic index (MI) was determined for each tumor, defined as the number of mitoses per 50 high-power microscopic fields. Only gastric and small intestine tumors had MIs more than 2. Tumors were treated by conservative excision in 67% and radical excision in 33%. At a median follow-up of 6 years there were no local recurrences. No patient with a tumor discovered incidentally has recurred. Three symptomatic patients have died of metastatic liver disease. Each patient with recurrence had a tumor with MI of 2 or more, which represents a recurrence rate of 16% in this group. We conclude that symptomatic gastric and small intestine tumors having two or more mitoses per 50 high-power fields carry a significant risk for recurrence, and that routine pathologic assessment of MI may identify a subset of patients who would potentially benefit from close follow-up and consideration for further therapy.

BENIGN SMOOTH MUSCLE tumors of the gastrointestinal (GI) tract are uncommon entities. Symptoms occurring because of size, location, and manifestations of bleeding may prompt diagnostic evaluation, but many tumors are discovered incidentally and are resected during laparotomy for other indications. Previous studies suggest that leiomyomas with benign gross and microscopic appearance may behave in an aggressive manner, making the assessment of the ultimate malignant potential of individual tumors difficult.[1-3] We reviewed the clinical experience and independently reassessed the surgical pathology of GI smooth muscle tumors seen at the Massachusetts General Hospital during the last 24 years to gain insight into the biologic behavior and appropriate management of such lesions.

Materials and Methods

The medical records of 131 patients diagnosed with benign GI smooth muscle tumors at the Massachusetts General Hospital between 1963 and 1987 were reviewed. Data obtained included patient sex, age at diagnosis, symptoms and physical findings leading to work-up, preoperative diagnostic evaluation, pathology reports, therapy, and further follow-up. A meticulous evaluation of specimens from the surgical pathology records was conducted independent of the clinical review. The number of mitoses seen in 50 high-power fields (HPF) was defined as the mitotic index (MI) for each tumor. Tumor size was assessed. Atypical tumors, considered to be from smooth muscle elements and not clearly sarcomas, were included. Epithelioid tumors were categorized with leiomyoblastomas. Follow-up information was obtained from the treating physician or directly from the patient. All records were included in the analysis of patient characteristics, but only those with a complete set of clinical information, pathologic data, and follow-up were considered evaluable cases for judging treatment. Outside slides sent for review and second opinion were not included unless complete clinical information and follow-up data were available.

Results

Patient Characteristics

One hundred thirty-one patients with benign GI stromal tumors were seen during the 24-year period. The median

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Accepted for publication: April 19, 1989.

age at time of diagnosis was 62 years (range, 19–89 years) with a slight male predominance (1.2:1). There were 103 evaluable cases in which a complete set of clinical, pathologic, and follow-up information was available. Three patients were excluded because of incomplete pathologic information. Recent follow-up information was unavailable for 25 patients.

Distribution of Tumors

As illustrated in Table 1, the majority of these tumors occurred in the stomach. Sites in order of decreasing frequency were small intestine, esophagus, rectum, and colon.

Clinical Presentation

Tumors were discovered before operation in two thirds of patients (Table 2). Esophageal lesions were symptomatic, primarily causing dysphagia and pain, in 80% of patients. Seventeen patients with gastric tumors and one patient with an esophageal tumor presented with acute hemorrhage. Three patients with small bowel tumors presented with gross bleeding, while four had more occult blood loss. Small bowel tumors presented with mechanical obstruction in only 8% of patients. Colorectal lesions generally caused no symptoms and were discovered on work-up of occult bleeding or incidentally.

Diagnostic Evaluation

Upper GI endoscopy identified 60% of gastric and 50% of esophageal lesions (Table 3), but results were abnormal in only 33% of patients with small bowel tumors. Contrast studies diagnosed all esophageal and 64% of gastric lesions in patients who were evaluated; however, small intestine lesions were seen in only 25% of small bowel studies. Computed tomography was useful in a small group of patients with gastric tumors. In two patients visceral arteriography detected small bowel tumors. Colonoscopy was more useful than barium enema for detecting colorectal lesions.

Pathology

Eighty-six per cent of tumors were benign leiomyomas. Other tumor types seen included 8 cellular leiomyomas, 6 leiomyoblastomas, 1 schwannoma, and 2 atypical, otherwise unclassifiable, smooth muscle tumors without sufficient characteristics to be called sarcomas. As shown in Table 4, 85% of tumors in this series were less than 5 cm in diameter. Eighty-four tumors had MIs of less than 2, while 19 demonstrated MIs between 2 and 7. MIs greater than 2 were seen only in gastric and small intestine tumors. All cases were originally diagnosed as benign lesions on the basis of standard light microscopy.

TABLE 1. *Site of Smooth Muscle Tumors*

Site	Number (%)
Esophagus	10 (8)
Stomach	81 (61)
Small intestine	25 (19)
Colon	7 (5)
Rectum	8 (6)

TABLE 2. *Clinical Presentation of Smooth Muscle Tumors*

Symptoms/ Signs	Percentage of Patients Affected				
	Esophagus	Stomach	Small Bowel	Colon	Rectum
Asymptomatic	20	31	44	57	29
Pain	36	20	24	0	13
Mechanical obstruction	55	0	8	14	0
Occult/frank bleeding	0	38	24	29	50
Dyspepsia	18	17	0	0	0

Therapy

All patients were treated by tumor excision, as described in Table 5. Excision with margins greater than 1 cm was performed in 34 patients (33%). No patient received adjuvant radiation or chemotherapy.

Follow-up

Information was available for 103 patients (81%). Median follow-up was 6 years; minimum follow-up was 1 year. There were three recurrences (Table 6). Tumors that recurred were all larger than 4 cm in diameter. Each was read as a benign leiomyoma on the basis of low-grade mitotic activity. Recurrence was associated with death of the three patients within 3 years after operation. There were no recurrences in patients with tumors having MIs less than 2. No recurrence of esophageal or colorectal tumors has been seen in this series.

TABLE 3. *Preoperative Evaluation*

Examination	Number Having Study (% positive)				
	Esophagus	Stomach	Small Bowel	Colon	Rectum
Endoscopy	8 (50)	52 (60)	9 (33)	7 (57)	6 (67)
Contrast studies	5 (100)	53 (64)	12 (25)	1 (0)	6 (33)
CT scan	0	6 (83)	1 (0)	0	0
Angiography	1 (0)	6 (50)	5 (40)	0	0

TABLE 4. *Tumor Characteristics*

	Tumor Diameter (cm)			Mitotic Index	
Site	<2	2–5	>5	0, 1	>2
Esophagus	2	6	1	9	0
Stomach	27	20	12	44	15
Small bowel	10	9	2	17	4
Colon	7	0	0	7	0
Rectum	7	0	0	7	0

TABLE 6. *Recurrences*

Site	Size	MI	Recurrence	Time to Death
Stomach	4 cm	7	liver	2 years
Duodenum	5 cm	2	liver	2 years
Jejunum	13 cm	4	liver	3 years

Discussion

Although uncommon, benign smooth muscle tumors of the GI tract can present diagnostic challenges. These lesions occur with greater overall frequency than do leiomyosarcomas (about 4:1), although two series have described a similar prevalence.[4,5] Such tumors arise most commonly from the muscularis propria or mucosae of the intestinal wall, but have also arisen from smooth muscle in the tunica media of blood vessels.[6] When local overgrowth of smooth muscle cells occurs in the muscularis, expansion may be toward the bowel lumen, the serosa, or both (dumbbell tumors), as illustrated in Figure 1.

Patients with smooth muscle tumors of the GI tract may be entirely asymptomatic or may manifest symptoms referable to tumor size, growth pattern, and location. In this series one third of the tumors were discovered incidentally. Upper GI lesions were responsible for dysphagia and epigastric pain in 70% of patients. Colorectal tumors were more likely to be discovered because of gross or occult bleeding. Because of lack of bleeding or encroachment on intestinal lumen, small, primarily extraluminal tumors rarely caused symptoms. Our report confirms the distribution by site of intestinal leiomyomas as reported in other series,[7,8] with the stomach and small bowel the most common.

Preoperative detection of these GI tumors is possible by contrast studies that may define a well-circumscribed luminal defect. Endoscopy may show ulcerated or raised mucosa overlying a tumor mass.[9] CT scanning[10] and visceral arteriography[11,12] may be useful, particularly for gastric and small intestinal lesions without an endoluminal component.

Pathologists have long been aware of the difficulties in differentiating benign from malignant smooth muscle GI tumors, which can be the case for soft-tissue leiomyomas in other locations. Although the mitotic activity of a GI stromal tumor remains the most critical prognostic factor, tumors have been seen to recur locally and to metastasize even with rare or absent mitotic figures.[13] According to Golden and Stout,[2] "one can never be entirely certain that any leiomyoma is necessarily benign, except the small

TABLE 5. *Surgical Therapy*

	Margin of Excision		
Site	<1 cm	>1 cm	No. of Recurrences
Esophagus	7	2	0
Stomach	40	19	1
Small bowel	12	9	2
Colon	4	3	0
Rectum	6	1	0

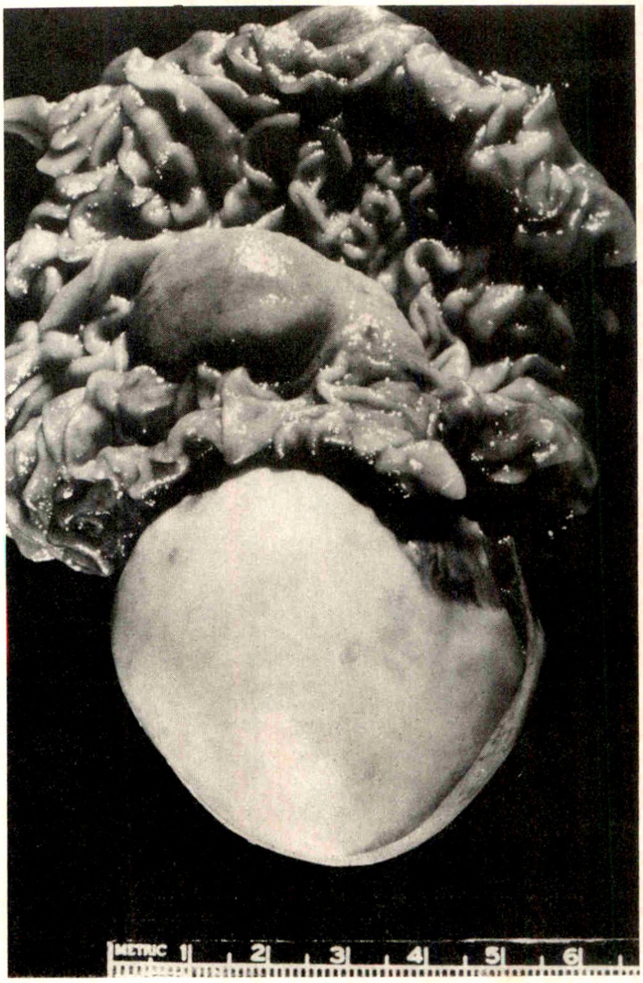

FIG. 1. Dumbbell leiomyoma of small intestine, illustrating both intraluminal and extraluminal components. In this instance, the extraluminal component predominates.

intramural tumors that are chance findings at autopsy or operation." They favored the designation malignant leiomyoma in this setting instead of sarcoma to denote a lesion with a lower degree of malignant potential. Ranchod[14] emphasized the importance of considering new criteria for the diagnosis of leiomyosarcoma in nonuterine smooth muscle tumors and believed that five or more mitoses per 10 HPF in gastric and small bowel tumors were indicative of malignancy. Appleman and Helwig[3] and Akwari[15] found that tenand five mitoses per 50 HPF, respectively, indicated a tumor with malignant potential. In the former series, 13% of patients with gastric leiomyomas with one to five mitoses per 50 HPF developed metastases.[16] In the current series, 3 of 19 patients (16%) with 2 or more mitoses per 50 HPF died of metastatic liver disease.

Gastric and small bowel leiomyomas with benign gross appearance have the potential, as seen in this study, to be aggressive lesions. Our only recurrences were in this group, and one fourth of gastric and small bowel tumors had MIs more than 2. No tumor involved lymph nodes, making regional node dissection not a necessary component of therapy.[8] In this study we observed no local recurrences, regardless of margin of surgical excision. Tumors with adherence to adjacent structures should be treated with *en bloc* resection of the adjacent structure to achieve excision of the entire tumor. For these tumors, this sort of adherence is an uncommon finding. The most important factor allowing prediction of subsequent recurrence proved to be the mitotic index. Darling and Welch[17] reviewed 46 benign and 86 malignant small bowel tumors and noted that a preoperative palpable mass was almost always indicative of malignancy. A palpable mass was not seen in any of our patients. All tumors that recurred in our series were initially symptomatic. We found no recurrences in patients with tumors discovered incidentally at laparotomy. We recommend conservative local excision for tumors found incidentally both for diagnosis and for evaluation of mitotic activity.

Esophageal and colorectal tumors in this series were less common lesions, had low MIs, and were also not associated with recurrence, regardless of margin of excision. Conservative local excision should suffice as therapy.

We recommend a higher index of suspicion for the malignant potential of symptomatic gastric and small intestinal leiomyomas, particularly those that have more than two mitoses per 50 HPF.

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Anorectal Carcinoid Tumors

Is Aggressive Surgery Warranted?

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The management of large carcinoid tumors of the anorectum is controversial. Most carcinoid tumors of the rectum and anus are early lesions, adequately treated by local excision. However, because of their relative rarity, the number of advanced cases seen at most institutions is small. Forty-three patients with anorectal carcinoid tumors were treated at our institution between 1960 and 1988 with complete follow-up. The median age of onset was 56 years. Eleven patients had no symptoms and the tumor was detected incidentally in eight additional patients with other diseases. Twenty tumors were larger than 2 cm in diameter and all patients had symptoms. Eight patients had another malignancy and three patients had ulcerative colitis. An association between ulcerative colitis and rectal carcinoid tumors is not widely appreciated. Eighteen tumors were treated by local excision, 16 by radical surgery, and nine underwent only biopsy. With complete resection of the primary lesion, local recurrence was never a problem. The median survival from diagnosis was 38 months in this series and 23 patients died of disease. After detection of metastases, the median survival time was 10 months. Tumors more advanced that T2 or larger than 2 cm in diameter were always fatal. All 13 patients with involved lymph nodes died of metastatic disease, with a median survival of 10 months, although one lived 9 years. Advanced rectal carcinoid tumors are aggressive malignancies. Adequate local excision controls regional disease but rectal carcinoid tumors are cured only when they are discovered before the T3 stage, measure less than 2 cm in diameter, and when lymph nodes are not involved. Consequently if a local excision permits complete resection, radical extirpative surgery will provide little benefit.

ALTHOUGH CARCINOID TUMORS of the anus and rectum represent only a small percentage of all anorectal tumors, they have excited considerable interest due to controversies surrounding their management. More than 600 cases have been reported, but only 12% were malignant and few series, therefore, discuss management of advanced anorectal carcinoid tumors.[1-3]

The Memorial Sloan-Kettering Cancer Center (MSKCC) experience with carcinoid tumors was reported in 1964.[4] The present series, representing patients seen between 1960 and 1988, differs from all previous reviews because many advanced cases have since been referred to Memorial Hospital. This permits analysis of these uncommon advanced anorectal carcinoid tumors.

Examination of the clinical presentation, treatment, pathologic stage, and outcome defines the role of aggressive surgery in the management of these cases.

Materials and Methods

Forty-eight patients with histologic diagnoses of anal or rectal carcinoid tumors were treated at MSKCC between 1960 and 1988. The medical and pathologic records were reviewed and the clinical presentation, examination, associated diseases, treatment, and outcome were noted. After pathologic review the patients were staged according to the 1987 recommendations of the American Joint Committee on Cancer (AJCC).[5] Five patients were excluded from the study due to inadequate follow-up data.

Survival was estimated by the method of Kaplan and Meier[6] with significance determined by the log-rank or chi square tests.

Results

The 48 patients with a diagnosis of anorectal carcinoid represent 30% of all gastrointestinal carcinoid tumors treated at MSKCC during this period, and 1.15% of all malignant anorectal tumors treated.

In the 43 patients included in this study there were 24 men and 19 women with a median age of 56 years. There was concomitant nonmalignant gastrointestinal disease

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in 12 patients, including three patients with ulcerative colitis. Five patients had synchronous tumors at presentation and three had a history of malignancy.

Clinical Presentation

Twenty-three (53%) patients had symptoms that were referable to the carcinoid tumor, nine (21%) had incidental symptoms, and 11 (26%) had tumors that were detected during screening of asymptomatic patients. Rectal bleeding, local pain, change in bowel habits, and weight loss were the most common symptoms referable to the tumor. Symptoms increased with tumor size and T stage (Table 1). The median duration of symptoms was 3 months (range, 1 to 48 months).

Two tumors arose in the anal canal and the remainder were equally distributed through the rectum at a median distance of 5 cm from the anal verge. Thirteen patients had hepatic metastases at presentation, and four had additional systemic metastases.

The three patients with ulcerative colitis were all younger than 35 years old, with long-standing inflammatory bowel disease. One of these carcinoid tumors was an incidental finding in the pathology specimen, but the other two patients presented with advanced lesions of the rectal stump after colectomy. Both died of disseminated disease.

Treatment

Sixteen tumors were confined to the submucosa (T1): 1 was only biopsied, 12 were treated by local excision, and 3 were included in surgical specimens from resections for carcinoma or colitis. Four tumors invading into, but not through, the muscularis propria (T2), were all treated by local excision. Nineteen patients had invasion into the subserosa or beyond (T3 or T4). Thirteen were treated by radical surgery and six by either local excision or merely biopsy. The T stage could not be determined in four patients because the biopsy material was inadequate.

TABLE 1. *Tumor Stage, Size, and Symptoms at Presentation*

	Symptoms	
T Stage*	Present	Absent
T1/T2	7	13
T3/T4	17	2

	Symptoms		
Size (cm)	Tumor	Incidental	None
<1.0	1	2	4
1.0–1.9	4	6	5
>2.0	17	1	2
Unknown	1		
Total	23	9	11

* $p < 0.0005$ by chi square test.

TABLE 2. *Tumor Size and Pathologic T Stage*

Size (cm)	T1	T2	T3/T4	Unknown	Total
0.1–0.9	6	1	—	—	7
1.0–1.9	10	2	1	2	15
>2.0	—	1	18	1	20
Unknown	—	—	—	1	
Total	16	4	19	4	

—, inadequate biopsy material.

Two patients with metastatic disease at presentation received portal vein chemotherapy and nine patients received various systemic chemotherapeutic regimens after recurrence.

Pathology

All pathologic material was examined at MSKCC, including that of five patients whose lesions were treated initially at other institutions. The diagnosis of carcinoid tumor was predicated on histologic morphology and immunohistochemical techniques were not routinely used.

Increasing tumor diameter was associated with greater invasion of the bowel wall (Table 2). In the 16 patients in whom node status could be ascertained: 4 had no nodal disease, 11 had 1, 2, or 3 positive nodes, and 1 patient had 9 involved nodes. No tumor less than 2 cm had lymph node metastases and all node-positive patients had symptoms.

Follow-up

The patients were followed for a median of 33.5 months (range, 0.5 to 226 months) with a median survival of 38 months. Survival was analyzed by symptoms, tumor stage, nodal involvement, and tumor size.

The median survival of patients with symptoms referable to their carcinoid tumors was 19 months. Their survival was much worse ($p < 0.001$) than that of patients with incidentally discovered lesions, the majority of whom survived (Fig. 1).

No patients with a carcinoid tumor confined to the submucosa (T1) died of disease but one of four patients with tumor infiltrating the muscularis propria (T2) died of disease. Their survival rate was significantly better ($p < 0.001$) than that of patients with deeply invasive tumors (T3 and T4) whose median survival was only 6.7 months (Fig. 2).

There was no significant difference in survival between patients with tumors less than 1 cm in diameter and those with tumors 1 cm to 2 cm in diameter. Three of these 23 patients (13%) died of disease (Fig. 3). Patients with tumors greater than 2 cm in diameter had a much worse prog-

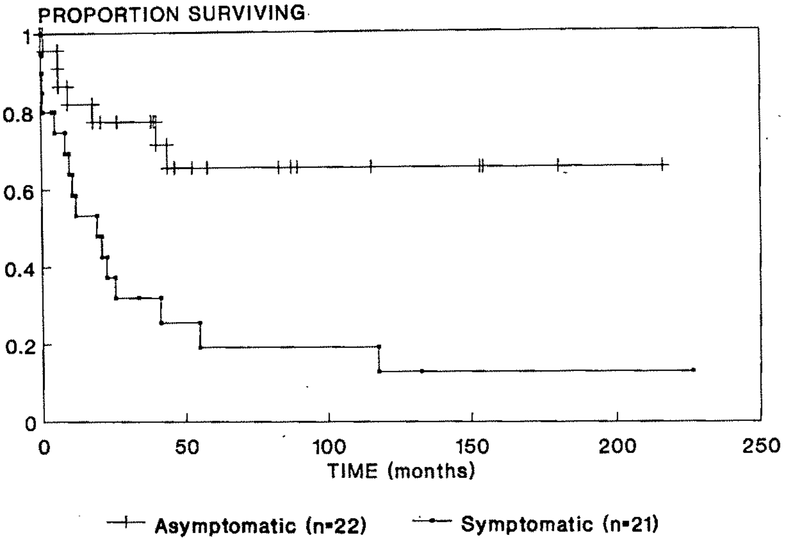

FIG. 1. Survival of asymptomatic patients (+) was significantly better ($p < 0.001$) than that of symptomatic patients (●).

nosis, and all died of disease with a median survival time of 6.7 months ($p < 0.001$).

Patients with involved lymph nodes demonstrated a median survival of 10 months, while most patients without nodal metastatic disease survived (Fig. 4).

Recurrence

Twenty-three patients died, with only one local recurrence. The liver was the most common site of failure with lung, brain, and bone metastases also represented. One patient had stable hepatic disease for 18 months but the remaining patients had progressive disease. The median survival after recurrence was 4.5 months. Treatment with chemotherapy did not influence survival.

Discussion

The pattern of patient referral to MSKCC may increase the incidence of associated malignancies, but the age, sex distribution, and associated pathology of these patients with anorectal carcinoid tumors are comparable to those reported in other series.[1-3] Only small numbers of advanced lesions are included in previous reports and consequently study of these tumors has been based on collected reviews.[1,7] The present series is noteworthy because a substantial number of patients with advanced disease have been treated at a single center.

The association of anorectal carcinoid tumors with other gastrointestinal tract malignancies has been appreciated,[1] but the possible association with ulcerative colitis is not widely appreciated.

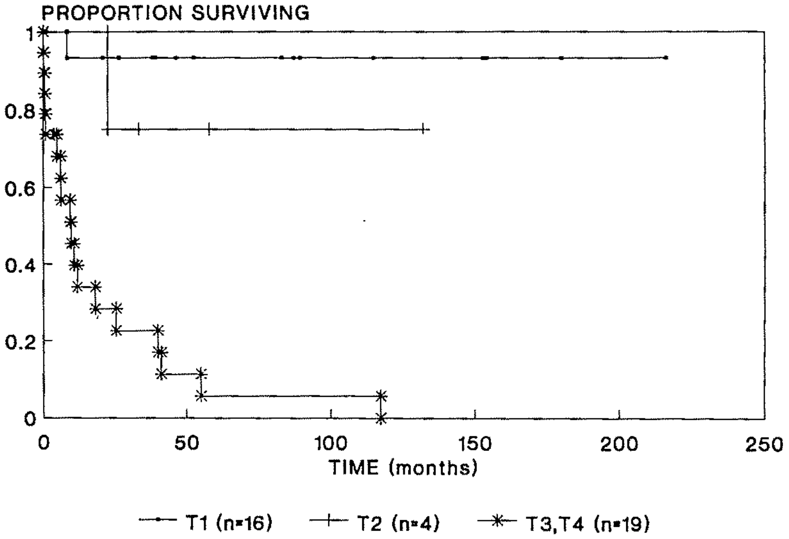

FIG. 2. Survival of patients with tumors confined to the submucosa (●) or to the muscularis propria (+) was significantly better ($p < 0.001$) than that of deeply invasive lesions (*).

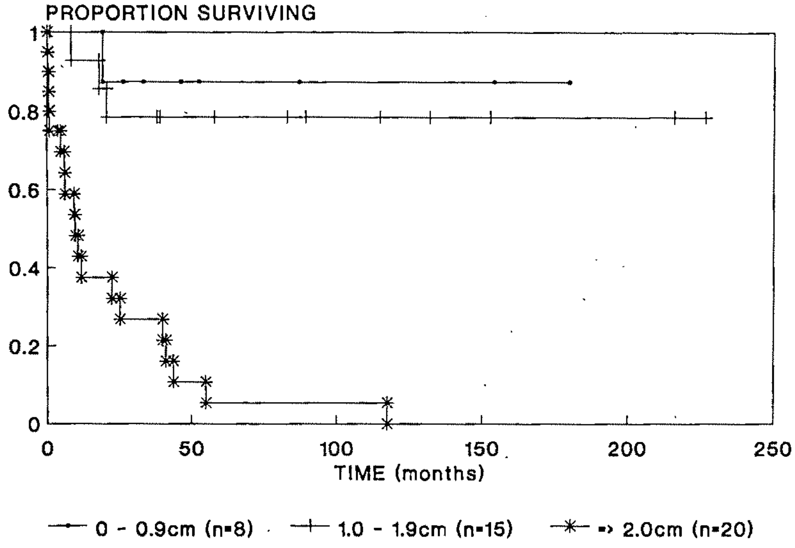

FIG. 3. Survival of patients with tumors less than 1 cm (●) or less than 2 cm (+) was significantly better ($p < 0.001$) than that of those with larger tumors (*).

Some authors distinguish benign from malignant carcinoid tumors on the basis of their histologic or cytologic appearance.[8] Gould and coworkers[9,10] propose that only well-differentiated, nonmetastasizing tumors should be described as carcinoids, and that the remaining tumors should be designated neuroendocrine tumors (analogous to lung lesions). They suggest that many neuroendocrine tumors have been misdiagnosed as poorly or undifferentiated neoplasms, atypical carcinoids, or small-cell tumors. In the present series seven patients had small-cell, undifferentiated lesions, several of which were initially considered anaplastic carcinoma (until immunohistochemical studies were performed). However the spectrum of clinical behavior seen here is predicted predominantly by size and depth of invasion and the majority of deaths occurred in patients with less ominous histology. Similar findings have been noted in carcinoid tumors from other sites.[3]

Symptomatic carcinoid tumors are highly aggressive lesions with a median survival time of 19 months in patients with symptoms referable to the carcinoid itself. However complaints associated with synchronous conditions (such as ulcerative colitis) should be distinguished from those due to the tumor alone.

There is a close association between tumor size and stage, so small tumors, less than 1 cm, should be treated by complete local excision. Their nature may not be recognized before surgery, but the risk of unfavorable outcome is small: 23 tumors treated by punch biopsy alone in one series[11] did not recur locally, although three patients were lost to follow-up. The rare local recurrence does not preclude surgical salvage.[1]

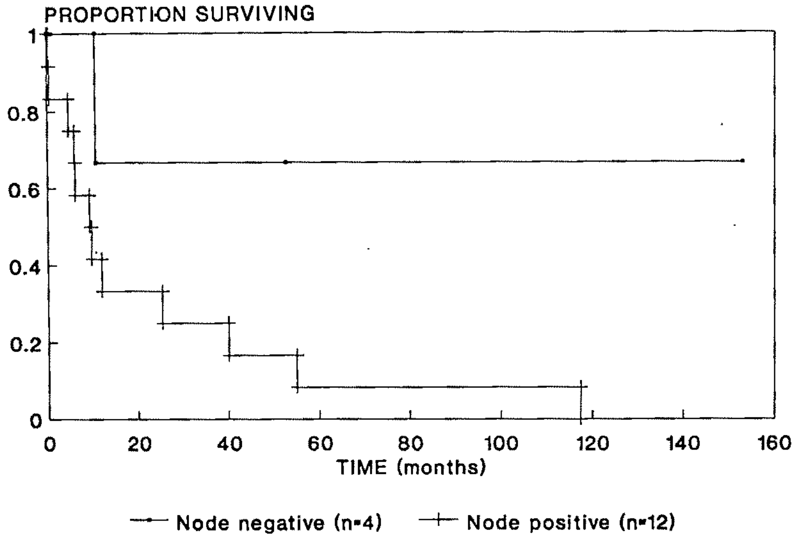

FIG. 4. Survival of patients with (+) and without involved nodes (●).

Almost all previous authors have recommended radical surgery for tumors larger than 2 cm in diameter. In this series, despite one 10-year survivor, all such patients died of disease with a median survival of only 6.7 months. Increasing the extent of resection by radical surgery in this setting is unrewarding. The median survival time was 10 months after abdominal–perineal or low anterior resection for tumors larger than 2 cm. No patients were cured by radical surgery and local failure was not a problem if the tumor was amenable to local resection at presentation.

Naunheim,[1] in a large retrospective review, estimated that 11% of tumors measuring 1 cm to 1.9 cm in diameter developed metastatic disease, and in the current series tumors invading only the muscularis propria (T2) are seldom fatal. All four tumors of intermediate size that invaded into the muscularis propria were treated in this series by local excision alone, and only one died. Because radical surgery does not cure patients with regional disease, adequate local excision should be the treatment of choice in patients with tumors between 1 cm and 2 cm in diameter.

Early carcinoid tumors are cured by local excision and advanced lesions are fatal regardless of the extent of resection. There is no apparent role for radical extirpative surgery in the management of anorectal carcinoids if the entire tumor can be removed by local excision.

Acknowledgment

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Different Lymphocyte Compartments Respond Differently to Mitogenic Stimulation After Thermal Injury

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Because of the association between the development of an immunocompromised state and an increased risk of infection, increasing attention has been focused on describing and characterizing the immune consequences of thermal injury. Results of human studies are largely based on the *in vitro* responsiveness of peripheral blood leukocytes, while splenocytes are generally used in the animal studies. Because the response of lymphocytes from different lymphocyte compartments may vary, we compared the responses of murine peripheral blood, splenic, Peyer's patch, and mesenteric lymph node lymphocytes to a battery of mitogens after thermal injury. Burn-induced immunosuppression was maximal in the splenic lymphocyte compartment, where the responses to all three test mitogens were depressed throughout the 28-day postburn study period. Although the PHA-induced mitogen response of lymphocytes from the other three lymphoid compartments remained suppressed throughout the study period, the response to the mitogens Con-A and PWM generally returned to normal or supranormal levels by the seventh postburn day. Therefore it appears that the effect of a thermal injury on lymphocyte function varies according to the lymphocyte compartment examined and the mitogen tested. These results raise the question of whether animal studies using splenic lymphocytes can be correlated with human studies performed on circulating blood lymphocytes.

FAILURE OF THE immune system leading to an increased susceptibility to infection is a major cause of morbidity and death of the burn victim.[1] For this reason, during the past two decades, a tremendous effort has been given to investigating the mechanisms promoting burn-induced immune failure. These studies have used human burn victims and animal models. Most of the animal studies have been performed in rodents because the immune system of the rodent has been well characterized, large numbers of animals can be studied at a reasonable cost, and the technical demands of inflicting a thermal injury in the rodent are minimal. However one major difference between these animal and human studies, which has received little attention, is that conclusions on the effects of thermal injury on cell-mediated immunity are based on studies of peripheral circulating leukocytes in humans, while splenocytes are generally studied in the murine models. Yet the response of lymphocytes from anatomically different compartments to the same stimulus can differ.[2,3] Furthermore the responses of B and T cells to antigen *in vivo* take place largely in lymphoid tissue, not in the bloodstream.[3] Thus it is important to know whether the response of circulating peripheral lymphocytes to a thermal injury is similar to that seen in splenic lymphocytes. In addition, because gut barrier failure leading to bacterial translocation has been documented to cause systemic infection in burned mice and rats,[4-6] studies of intestinal immunity after thermal injury are also important. Therefore the goal of the present study was to measure and compare simultaneously the blastogenic response of peripheral blood, splenic, and gut-associated lymphocytes to a battery of mitogens in a murine burn model.

Materials and Methods

Mice

Seven-to-10-week-old, specific pathogen-free, inbred Balb/c mice of both sexes weighing 24 g to 32 g were used in these experiments. Inbred Balb/c mice were chosen for study because variability between animals is reduced in inbred compared to outbed strains. The mice were housed under barrier-sustained conditions and maintained in accordance with the recommendations of the Guidelines

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for the Care and Use of Laboratory Animals. The experiments were approved by the LSU-Medical Center Animal Care Committee.

Thermal Injury

The mice were burned according to the procedure described by Walker et al.[7] The mice were anesthetized with intraperitoneally administered sodium pentobarbital (0.4mg/10 g of body weight). The hair was removed from the back and the mouse was placed in a plastic holder containing a 2.5 × 3.5 cm^2 opening to allow exposure of the animal's back to the boiling water. The exposed back was immersed in boiling water for 5 seconds to produce a 25% total body surface area (TBSA) third-degree burn. The mice were immediately resuscitated with 2 mL of intraperitoneally (IP) administered sterile saline.

Cell Preparation

Mice were sacrificed 1, 3, 5, 7, 14, or 28 days after burn and peripheral blood, spleen, mesenteric lymph node, and Peyers patch mononuclear cells were isolated as follows. After the mice were anesthetized with IP sodium pentobarbital, the thoracic cavity was opened aseptically with sterile instruments. Approximately 1 mL of blood was collected in heparin (100 units) by cardiac puncture. An abdominal incision was then made and the spleen and the mesenteric lymph node complex were removed and placed in cold (4 C) minimal essential medium (MEM) supplemented with 2mM L-glutamine and containing 100 U/mL of penicillin, 100 μg/mL of streptomycin, and heat-inactivated fetal calf serum (2% v/v). After these organs were removed, the small intestine containing the Peyers patches was excised.

Peripheral blood mononuclear cells were isolated as follows. The blood was mixed with 1 mL of MEM supplemented with 2mM L-glutamine and containing 100 U/mL of penicillin, 100 μg/mL of streptomycin, and heat-inactivated fetal calf serum (2% v/v). The blood-modified MEM mixture was layered over 1.5 mL of ficol-hypaque and centrifuged for 15 minutes at 1200 to 1500 RPM. The mononuclear cell interface was collected and washed twice with modified MEM. The washed cell pellet was incubated in 1 mL of 0.14 M ammonium chloride for five minutes at 37 C to lyse contaminating erythrocytes. The mononuclear cells were then washed twice with modified MEM, counted, and resuspended in RPMI 1640 containing 2 mM L-glutamine, 100 U/mL of penicillin, 100 μg/mL of streptomycin, and 10% v/v fetal calf serum at a final concentration of 4×10^6 cells per milliliter. Cell viability was more than 95% by trypan blue dye exclusion.

Splenic mononuclear cell populations were obtained by sieving the spleen through sterile 100-gauge stainless steel wire mesh. The single cell suspensions were washed twice with modified MEM and adjusted to a final concentration of 4×10^6 cells/mL in RPMI 1640 containing 2 mM L-glutamine, 100 U/mL of penicillin, 100 μg/mL of streptomycin, and 10% v/v fetal calf serum. Viability was verified by trypan blue dye exclusion.

The mesenteric lymph nodes were gently minced and then passed through three layers of sterile rayon/polyester gauze to create a single-cell suspension. The single-cell suspension was washed three times with modified MEM and adjusted to a final concentration of 4×10^6 cells/mL in RPMI 1640 containing 2 mM L-glutamine, 100 U/mL of penicillin, 100 μg/mL of streptomycin, and 10% v/v fetal calf serum. Viability was verified by trypan blue dye exclusion.

The Peyers patches were excised from the serosal side of the intestine with care being taken not to enter the lumen. The Peyers patches were then teased apart with sterile forceps and further fragmented by gentle pipetting. Approximately five to seven Peyers patches were obtained from each animal. The fragments were treated with type 1 collagenase (50 U/mL) in modified MEM for 60 minutes at 37 C.[8] After collagenase digestion, the cell suspension was passed through three layers of sterile rayon/polyester gauze and subsequently washed three times in modified MEM. The cell suspension was adjusted to a final concentration of 4×10^6 cells/mL in RPMI 1640 containing 2 mM L-glutamine, 100 U/mL of penicillin, 100 μg/mL of streptomycin, and 10% v/v fetal calf serum. Viability was verified by trypan blue dye exclusion.

Mononuclear cell preparations from the blood, spleen, mesenteric lymph nodes, or Peyers patches were placed into microtiter plates. The blastogenic responses of these cell cultures (2×10^5 cells) were tested using the following mitogens: phytohemagglutinin (PHA) (1 μg), concanavalin A (Con-A) (2.5 μg), or pokeweed mitogen (PWM) (5 μg). PHA and Con-A are primarily T-cell mitogens and PWM is primarily a B-cell mitogen, although none of these agents affect one cell population exclusively.[9] Simultaneous cell cultures were run in the absence of mitogen stimulation. The cells were incubated for 72 hours in 5% CO_2 at 37 C, pulsed with 0.5 uCi of tritiated thymidine, and incubated an additional 18 hours. The cells were harvested with a cell harvester and counted in a scintillation counter. Each assay was run in triplicate and the results were averaged and the mean value was used for statistical analysis.

Statistics

Comparisons between groups were analyzed using analysis of variance (ANOVA) with the Newman-Keuls test. Statistical significance was considered to be achieved at $p < 0.05$.

Results

Table 1 illustrates the blastogenic response of blood, splenic, mesenteric lymph node (MLN), and Peyers patch lymphocytes to the three test mitogens. The blastogenic responses of lymphocytes from these four lymphocytes compartments varied in their ability to respond to the different mitogens and in the magnitude of their responses. The most responsive lymphocyte population was the splenic lymphocytes, followed by the MLN, blood, and Peyers patch lymphocytes. Of the mitogens tested, Con-A induced the greatest blastogenic response by all four lymphocyte populations. These results indicate that peripheral blood lymphocytes do not respond as well to mitogens (at the doses tested) as splenic or MLN lymphocytes. Although the blastogenic response varied among the lymphocyte populations, the level of tritiated thymidine uptake by unstimulated cells was similar among all four lymphocyte populations.

As described by others,[10,11] the response of splenic lymphocytes to mitogens was severely depressed after a thermal injury (Fig. 1). Three days after burn, the blastogenic response of the splenic lymphocytes to all three mitogens was significantly depressed. Although the blastogenic response of the splenic lymphocytes was returning toward normal, it remained significantly depressed even 28 days after burn. The pattern of spontaneous thymidine incorporation by the splenic lymphocytes differed from the mitogen-stimulated response. Spontaneous blastogenesis was decreased three and five days after burn, however, in contrast to mitogen-stimulated blastogenesis, spontaneous blastogenesis, which was significantly increased seven and 14 days after burn.

The blastogenic response of the peripheral blood lymphocyte population differed from the splenic population in several ways. First spontaneous blastogenesis of the circulating lymphocytes was increased by day 3 after burn and remained increased through day 14 after burn (Fig. 2). Second although the PHA response of the circulating lymphocyte population remained depressed throughout the 28-day postburn period, and thus was similar to the splenic response, the response of the circulating blood lymphocytes to Con-A and PWM differed from that found in the splenic population. The suppressive effect of a thermal injury on the blastogenic response to Con-A and PWM was shorter lived in the peripheral blood lymphocytes than in the splenic lymphocytes. Seven days after burn the circulating lymphocyte response to Con-A or PWM was normal or increased and remained normal throughout the study period. Thus the spontaneous and stimulated blastogenic responses after thermal injury were not identical between circulating and splenic lymphocytes.

The pattern of mitogen-stimulated blastogenesis of the MLN lymphocyte population was similar to the pattern found in the peripheral blood lymphocytes (Fig. 3). The PHA response remained depressed for the 28-day study period, while the burn-induced depression of lymphocyte blastogenesis to Con-A or PWM was complete by the seventh postburn day. The spontaneous blastogenic response of the MLN lymphocytes was normal at all time points.

The pattern of mitogen-stimulated blastogenesis of the Peyers patch lymphocytes was similar to that found in the peripheral blood lymphocytes, with the exception that the response to Con-A or PWM was greater than normal on day 28 postburn (Fig. 4). The pattern of spontaneous blastogenesis was similar to that found in the spleen with an early decrease in blastogenesis followed by increased levels of thymidine incorporation.

Discussion

The major finding of this murine study is that the effect of a thermal injury on lymphocyte function varies based on the lymphocyte compartment examined, as well as on the mitogen tested. Thus our results are consistent with the recent experimental studies of Burleson et al.[12] on the effects of a thermal injury on lymphocyte subpopulation levels. These authors found that the ratio of T-helper to T-suppressor/cytotoxic lymphocytes from blood, spleen, and lymph nodes of burned and burned-infected rats varied based on the lymphocyte compartment measured. Although measurements were made only at one time (two days after burn), it was clear that lymphocyte subpopulation changes after burn and infection were different for each tissue tested.[12] The effect of thermal injury on different lymphocyte compartments in humans has not been studied; however the blastogenic response of peripheral blood lymphocytes to different mitogens has been shown to vary in humans sustaining thermal injuries.[13,14]

Although *in vitro* assays of mononuclear cell function and activity were developed to study cell-mediated immunity, use of these assays to elucidate the immune state

TABLE 1. *Comparison of Mitogenic Response Between Mononuclear Cell Populations Isolated from Different Lymphocyte Compartments*

Mononuclear Cell Source	n	Media	PHA	Con-A	PWM
Blood	14	277 ± 85	3002 ± 707	6617 ± 1634	2637 ± 583
Spleen	14	305 ± 51	6387 ± 1420	68,567 ± 10,851	15,034 ± 3916
MLN	14	324 ± 93	4278 ± 720	30,548 ± 5877	5181 ± 689
Peyers patches	14	270 ± 64	502 ± 84	2613 ± 877	634 ± 125

Data expressed as mean ± SD tritiated thymidine uptake in disintigrations per minute (DPM).

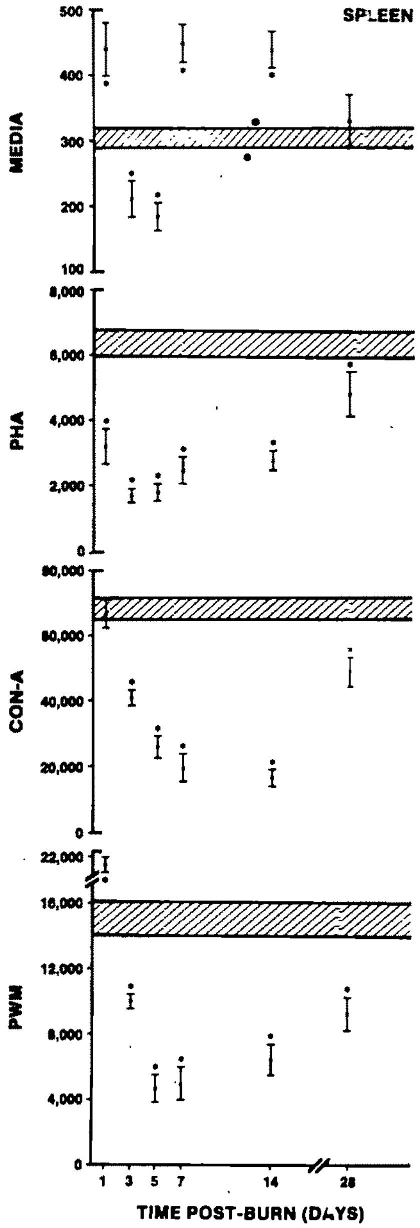

FIG. 1. Response of unstimulated and mitogen-stimulated (PHA, CON-A, PWM) splenic lymphocytes harvested from 1 to 28 days after thermal injury. All values expressed as mean ± SEM DPMs of tritiated thymidine uptake. Hatched bar represents control lymphocyte incorporation of tritiated thymidine (mean ± 1 SEM).

* Indicates that experimental value is different ($p < 0.05$) from control value by ANOVA.

of the burn patient has been confusing. Using the blastogenic response to PHA as an example, some authors have reported an increased mitogenic response in burn victims,[15,16] while others have reported a blunted[17-19] or normal mitogenic response[20] in burn victims. In addition some investigators have reported that the cellular response to PHA correlates with sepsis and/or death[21,22] while others have not.[17,20,23] Part of the difference between these previously reported studies may be related to differences in mononuclear cell preparation, techniques of performing the *in vitro* mitogen assay, or patient selection. In fact recent human[24-26] and animal[27] studies have documented that density gradient purified peripheral blood mononuclear cells from burn victims but not normal controls are contaminated with many nonlymphoid cells. Furthermore recently we have demonstrated that the presence of these contaminating leukocytes causes artifactual alterations in standard *in vitro* tests of lymphocyte function.[24] These human studies emphasize the difficulties of assessing the global systemic immune state of burn victims based on measurements of just one lymphocyte compartment.

In contrast to these human studies, the splenic response

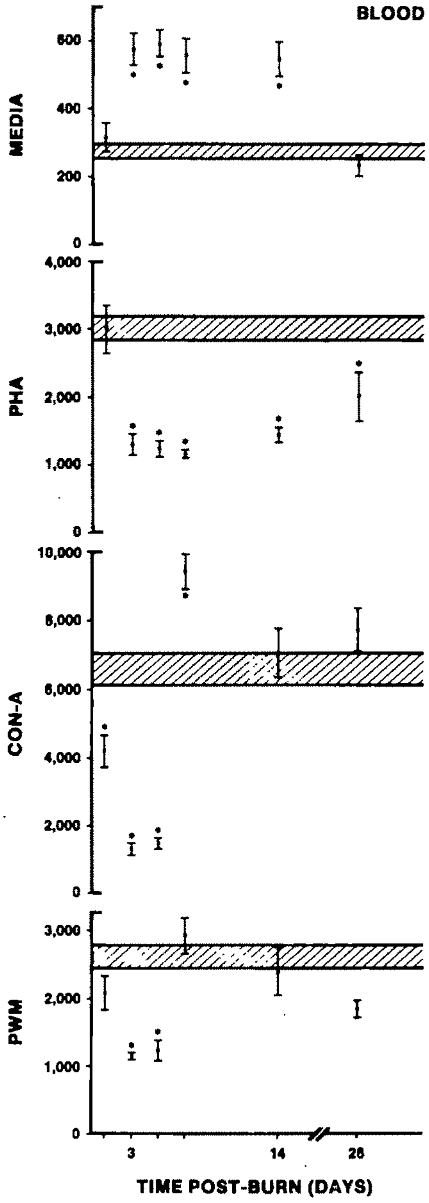

FIG. 2. Response of unstimulated and mitogen-stimulated peripheral blood lymphocytes. See Figure 1 legend for details.

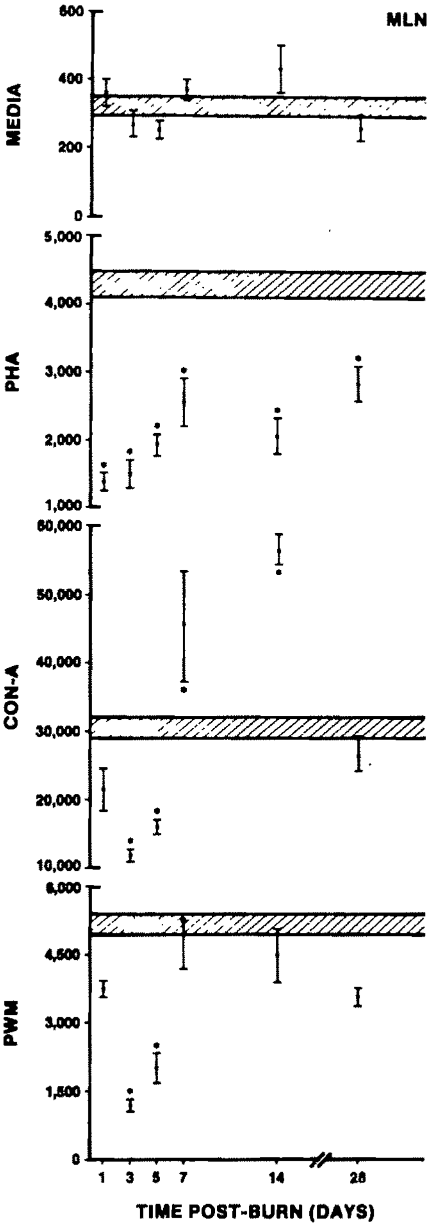

FIG. 3. Response of unstimulated and mitogen-stimulated mesenteric lymph node lymphocytes. See Figure 1 legend for details.

to different soluable and cellular blastogenic stimuli has been an accurate predictor of global immune competence after thermal injury in animals.[28,29] One explanation for this fact may be that the splenic response to stimuli more closely reflects the immune state of the burned animal than the response of other lymphocyte compartments. This explanation is supported, at least in part, by our results documenting that of all the lymphocyte compartments tested, the blastogenic response of splenic mononuclear cells was the most consistently impaired.

With the development of recombinant DNA technology, it has become possible to produce large quantities of purified endogenous biologic response modifiers, such as IL-1, IL-2, gamma-Interferon, and colony-stimulating factors. Many of these factors have been tested in murine burn models and shown to improve survival and bolster various arms of the immune system, especially the response of splenic mononuclear cells.[30-32] Thus it is possible that these biologic response modifiers may be effective in improving host immune defenses in burn victims and thereby improve survival. However, because in humans only peripheral blood lymphocytes can be sampled, and the mitogenic response of peripheral blood lymphocytes may not fully reflect the immune state, it may be difficult to monitor the immunomodulating effects of these agents in clinical practice. Our finding that the blastogenic response of peripheral blood and splenic lymphocyte populations may vary demonstrates the potential difficulty of

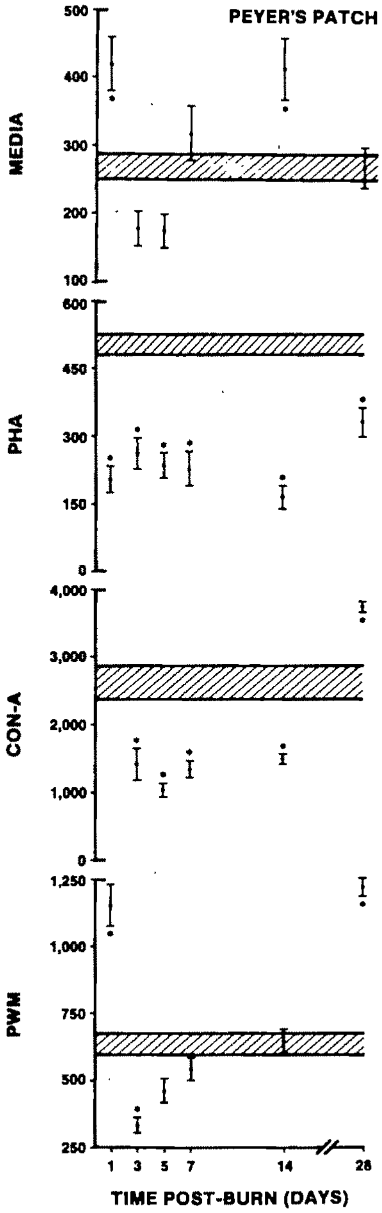

FIG. 4. Response of unstimulated and mitogen-stimulated Peyer's patch lymphocytes. See Figure 1 legend for details.

accurately monitoring immune competence by measuring just the response of peripheral blood lymphocytes.

Because intestinal antibacterial barrier function fails after thermal injury, resulting in the translocation of intestinal bacteria to systemic organs,[4,5] we also measured the effect of a thermal injury on intestinal immunity. To our knowledge these are the first studies to investigate whether the response of Peyers patch or MLN lymphocytes to mitogens are altered after thermal injury. The results of these studies indicate that the blastogenic response of Peyers patch and MLN lymphocytes are impaired after thermal injury. The overall patterns of response of lymphocytes from these two lymphocyte compartments were similar but not identical. In both compartments the blastogenic response to Con-A and PWM returned to normal by 28 days after burn, while the blastogenic response to PHA remained depressed throughout the study period. Thus the mitogenic responses of Peyers patch and MLN lymphocytes after thermal injury were similar to the general response of peripheral blood lymphocytes and different from splenocytes. The clinical significance of these findings are speculative. However the fact that intestinal immunity is abnormal after a nonlethal thermal injury is consistent with our previous studies documenting that thermal injury promotes bacterial translocation in Balb/c mice.[33]

These studies demonstrate the compartmentalized response of different lymphoid tissues to mitogens after thermal injury. Further studies are needed to determine the potential biologic and clinical significance of these findings.

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Ibuprofen in Acute-Care Therapy

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Ibuprofen is a potent cyclooxygenase inhibitor known to reduce the production of arachidonic acid metabolites. Prostacyclin and thromboxane are well-studied metabolites that play a prominent role in inflammation. Many of the effects of ibuprofen can be linked to its anti-inflammatory properties. Beneficial results from ibuprofen therapy have been documented, and more widespread use of the drug seems indicated. Conditions ranging from immunologic response to trauma and sepsis to postburn lung dysfunction to wound edema are improved by the use of ibuprofen. The fact that ibuprofen is effective in the various conditions detailed above, while other steroidal and nonsteroidal drugs are effective only in selective instances, increases the value of ibuprofen. Other properties of the drug, aside from its anti-inflammatory effects, are not as well studied and not as well known. Their importance, however, should not be overlooked. Superoxide radical tissue injury may be very important in acute injury and this phenomenon needs further study. In several studies ibuprofen has been shown to antagonize this type of injury. Similarly fibrinolysis inhibition is known to occur in burn wounds, but its role in other injuries is unknown. The antagonism of this inhibitor by ibuprofen maintains vascular patency. The clinical use of ibuprofen will increase as research further elucidates the mechanisms of tissue injury in acute situations and the many and varied mechanisms of action of ibuprofen.

NONSTEROIDAL ANTI-INFLAMMATORY drugs (NSAID) have assumed an important pharmacologic role in the treatment of inflammatory diseases. While several uses for the drugs have been found, rheumatic diseases remain the most common conditions for which they are used. NSAID in general, and ibuprofen in particular, have been shown to have beneficial effects on various acute conditions ranging from sepsis, to traumatically induced pulmonary damage, to wound healing.

Inflammation is manifested in varying complex responses and may be induced by various stimuli.[1,2] Most NSAID affect processes common to inflammation resulting from different causes.[3,4] These processes include phagocytosis, lysosomal release of enzymes, chemotactic stimuli, and the activation of the clotting, fibrinolytic, kinin, and complement pathways. Certain mechanisms may be more important in different tissues and different inflammatory responses.

Inhibition of cyclooxygenase, an important enzyme in the biosynthesis of prostaglandins, is a prominent action of NSAID. Arachidonic acid is released from phospholipids and is converted to endoperoxides by cyclooxygenase. The prostaglandins, thromboxane and prostacyclin, are the end products of the arachidonic acid cascade.[5] These substances are important in platelet physiology[6] and they modulate cellular responses to many stimuli, including bacterial products, cytokines, and tissue fluid components generated by the inflammatory response.[2,3,7]

In the production of some endoperoxides by cyclooxygenase, the free radical superoxide is formed. This substance is converted to the hydroxyl free radical. Both these strong oxidizing agents damage tissue during inflammation.[8] These free radicals are also byproducts of the respiratory cycle of neutrophils and macrophages during phagocytosis, and the byproducts of the inflammatory cells' responses to chemotactic stimuli.[8] Superoxide generation is inhibited by a number of NSAID at chemical levels comparable to those achieved therapeutically.[9]

Aside from inhibiting prostaglandin biosynthesis, NSAID inhibit phosphodiesterase, thus raising the intracellular concentration of cyclic AMP (cAMP),[10] which stabilizes membranes, including lysosomal membranes, in neutrophils. Enzyme release, which is significant in the inflammatory response, is prevented. By stabilizing the membrane and thereby decreasing lysosomal activity, cAMP also decreases the production of superoxide by phagocytes.[11]

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The effectiveness of NSAID is increased by their binding to serum proteins. Blood vessels in inflamed tissue permit the escape of high molecular-weight plasma proteins. NSAID associated with these proteins may reach a greater concentration in inflamed areas than in normal interstitial fluid.[5]

Effects of Ibuprofen

Ibuprofen has been shown to have beneficial effects in acute episodes on a wide range of tissues Ibuprofen was the first phenylpropionate to be marketed in the United States. It has analgesic, antipyretic, and anti-inflammatory activities[12] and it is well absorbed enterally[13] and well tolerated.[14] This review will examine the varying effects of ibuprofen on different tissues in acute or traumatic situations.

Immunology

Immunosuppression occurs frequently after major injury, contributing to infection and mortality in trauma patients. Preventing immunosuppression may lead to decreased infection and improved survival in patients. Prostaglandins, locally produced toxic materials resulting from trauma, and other substances are suspected immunosuppressive agents.

Initial studies showed that cell-mediated immune response (CMIR) was suppressed in burned mice but was significantly restored by ibuprofen or indomethacin.[15] Delineation of lymphocyte subpopulations in burned mice by monoclonal antibodies showed that the ratio of helper to suppressor cells decreased from a control level of 3.13 to 1.77 14 days after burn. Intraperitoneal postburn treatment with ibuprofen or indomethacin restored the lymphocyte ratio to normal levels.[16]

Further study broadened the range of induced trauma. Liver resection, 20% body surface area burn, and crush-amputation hind limb injury were studied in mice. All conditions caused a decrease in helper lymphocytes and an increase in suppressor lymphocytes Pretrauma administration of ibuprofen prevented alterations of the lymphocyte subpopulation in the crush-amputation injury group.[17]

Follow-up studies from the same group[18,19] showed that ibuprofen increased survival after a septic challenge. Burned mice had a 60% survival rate, while burned mice subjected to cecal ligature and puncture (septic challenge) had a 20% survival rate. Ibuprofen increased the survival rate after burn and septic challenge to 64.7%. The other study reported a survival of 63.8% after septic challenge alone, and a survival rate of 26.2% after hind limb crush injury and amputation and septic challenge. Ibuprofen restored survival rates for the last group to those of septic challenge alone.

Prostaglandins may be the cause of trauma-induced depression of the CMIR. PGE_2 production is elevated in burned individuals, while CMIR is depressed. Preservation of CMIR after burn injury was seen in mice treated with 40 mg/kg ibuprofen or treated with anti-PGE_2 antibody.[20] Inhibiting the production of PGE_2 by ibuprofen or neutralizing it with antibody both prevent burn-induced immunosuppression.

Ibuprofen has also been shown to restore the bactericidal activity of polymorphonuclear (PMN) leukocytes suppressed by thermal injury. Intramuscular ibuprofen administered to guinea pigs inhibited the production of 6-keto prostaglandin $F_{1\alpha}$ and thromboxane B_2 in wound fluid. The drug also restored the bactericidal activity of PMN to normal when challenged with *Pseudomonas aeruginosa.* Ibuprofen had no effect on systemic complement consumption, thrombocytopenia, leukocytosis, or leucopenia.[21] Improved PMN activity may be due to inhibited granulocyte aggregation. Therapeutic levels of ibuprofen produced dose-dependent inhibition of binding of ligand to specific receptors on the granulocyte surface. Receptor number and dissociation kinetics were unchanged. Slowing the rate of association of ligand to its surface receptor may account for the inhibited granulocyte aggregation produced by ibuprofen.[22]

Shock

Ibuprofen has beneficial effects in septic and hypovolemic shock in various animal models. Although the studies did not replicate each other in every detail, improvement was noted in each. The mechanism was not detailed in any study, but prostaglandin and thromboxane inhibition are very likely prominent factors. Prostaglandins released during inflammatory reactions cause increased microvascular hydrostatic pressure, a primary cause of edema and a contributing factor of hypovolemia. Thromboxane is a known platelet aggregator. Superoxide radicals also may be involved, but they were not studied.

Adams and Traber[23] studied the cardiopulmonary response of sheep to *Escherichia coli* endotoxin-induced shock. Ibuprofen given before and after endotoxin infusion reduced the magnitude of the microvascular hydrostatic pressure-induced edema and hypovolemia occurring in the early stages of endotoxin shock. Ibuprofen also reduced the magnitude of the decrease in PaO_2, PMN count, and lymph-to-plasma protein ratio. Late changes, however, were unaffected by the drug.

Several studies of canine endotoxin shock showed improvement using ibuprofen therapy. Almquist[24] showed that ibuprofen had no effect on early endotoxin shock, but improved hypotension and thrombocytopenia caused by pulmonary platelet trapping was noted two hours after treatment. A follow-up study[25] confirmed the reversal of hypotension by ibuprofen and, further, showed that methylprednisolone and ibuprofen together improved survival. Beck and Abel[26] found that ibuprofen, given 30 minutes after endotoxin infusion, returned decreased blood pressure and hepatic blood flow to normal levels in 15 minutes. Dogs treated with ibuprofen before endotoxin infusion did not suffer any hypotension or decreased hepatic blood flow. Hypoglycemia and the accumulation of lactate and glycerol in plasma were unaffected by ibuprofen, however. Jacobs et al.[27] noted an initial decrease in blood pressure in dogs treated with and without ibuprofen when challenged with *E. coli* endotoxin. By two hours, however, the ibuprofen-treated group had a systolic blood pressure of 150 mm Hg compared to 83 mm Hg in the untreated group. Ibuprofen also protected against acidosis and depression of cardiac index.

In a rabbit model ibuprofen had a favorable dose-dependent effect on Group B streptococcal shock and it significantly improved short-term survival.[28] In a canine hypovolemic shock model, ibuprofen showed greater benefit than normal saline infusion. Ibuprofen given 45 minutes after the induction of hypovolemic shock significantly increased mean arterial blood pressure and total peripheral resistance. No change in heart rate, cardiac output, left ventricle contractility, or survival was noted at 72 hours.[29] A beneficial effect of ibuprofen on shock is evident but its specific mode of action is not clear.

Neurology

Although not thought of primarily as a neurologic drug, two studies showed neurologic improvement after trauma using ibuprofen. Hall[30] assessed neurologic status in mice one hour after head crush injury. The mean grip test score in mice treated with ibuprofen increased 122% over mice treated with normal saline. No change was noted using a selective thromboxane A_2 synthetase inhibitor, a stable PGI_2 analog, or a selective 5-lipoxygenase inhibitor. Pappius and Wolfe[31] induced focal cortical freeze injuries that caused widespread depression of local cerebral glucose use (LCGU). Ibuprofen and indomethacin significantly improved LCGU when given six hours before freeze injury or up to 24 hours after freeze. Prostaglandins seem to be operant in this situation.

Cardiology

Several studies have shown the benefit of ibuprofen on myocardial infarct size and myocardial fibrosis. Romson et al.[32] induced left circumflex artery thrombosis in dogs by low amperage stimulation of the intimal surface. Oral ibuprofen prevented occlusive left circumflex thrombosis and reduced the developed thrombus mass by 50%. The infarcted left ventricular mass decreased from 24% to 1% of the mass of the heart. Scanning electron microscopy revealed minimal platelet adherence to the damaged intima in ibuprofen-treated animals. The extent of myocardial ischemic injury was reduced by ibuprofen in an occlusion-reperfusion model. The same group[33] replicated these findings while evaluating platelet aggregation and leukocyte infiltration during acute myocardial infarction in dogs. Myocardial infarct size and leukocyte accumulation were both reduced, although, in this study, platelet accumulation in infarcted myocardium, as measured by a radiolabelled platelet technique, was not altered by ibuprofen. A contrasting study[34] evaluated myeloperoxidase activity and PMN accumulation as indicators of myocardial infarct size. While ibuprofen did not alter those parameters, it did increase the incidence of hemorrhagic infarction and ventricular fibrillation.

Walinsky et al.[35] studied pacing-induced myocardial ischemia in humans. The group found that ibuprofen, given two hours before testing, stabilized lysosomal membranes and prevented platelet-activated release of thromboxane. Morbidity would presumably be reduced. In a canine model of myocardial ischemia, Michael et al.[36] also found that ibuprofen or prostacyclin prevented thrombocytopenia from platelet trapping and also prevented increased immunoreactive thromboxane.

Reeves et al.[37] found that ibuprofen and methylprednisolone each retarded the development of radiation-induced myocardial fibrosis, pericarditis, and pericardial effusion in rabbits. Overall survival rate was also improved. Ibuprofen seems to decrease cardiac injury in experimental animal models. The mechanism may be related to suppressed inflammatory response as suggested by the PMN and methylprednisolone data.

Pulmonary Response

A diverse collection of studies measured pulmonary responses to ibuprofen in various animal models. All but one showed significant improvement using the drug. Demling's group[38-41] studied pulmonary dynamics in sheep after burn injury. A 1985 study noted that burn injury caused increased lung transvascular fluid flux as measured by lymph flow, transient pulmonary hypertension, decreased lung compliance, and decreased PaO_2. Ibuprofen lessened the degree of lung dysfunction.[38] A follow-up study gave more details.[39] Dynamic lung compliance after burn injury decreased by 40% but no increase in lung water was found in postmortem analysis. Lipid peroxidation of lung tissue increased significantly, while venous thromboxane rose transiently, and plasma prostacyclin and lung lymph did not change. Ibuprofen attenuated the decrease in lung compliance and the increase in lung lipid peroxidation. Therefore it seems that altered lung compliance after a burn is not due to increased lung water, but rather to mediator-induced bronchoconstriction, which improves after the administration of ibuprofen. The mediator is most likely thromboxane or a byproduct of oxygen radicals.

Two other studies by the Demling group examined the pulmonary effects of the local injection of *E. coli* endotoxin beneath the eschar. Local production of thromboxane resulted in distant lung dysfunction. Both parameters were eliminated by subeschar injections of ibuprofen.[40] Intravenous and 5% topical ibuprofen were also examined. Intravenous administration eliminated increased pulmonary artery pressure and decreased mean arterial oxygen tension. The production of prostanoids by burned tissue did not increase, as in controls, and plasma prostanoids were decreased below baseline, a potentially deleterious effect. Topical ibuprofen also prevented lung dysfunction while plasma thromboxane levels remained at baseline. The bacterial wound count increased in topically treated wounds to 10^5 to 10^7 bacteria per gram of tissue compared to 10^2 to 10^3 per gram for dry, untreated burns. This is probably a result of softening of the burn.[41] Locally or systemically administered ibuprofen significantly improves postburn lung function.

Two adult respiratory distress syndrome (ARDS) models were improved by ibuprofen but not by methylprednisolone. Rinaldo and Dauber[42] subjected rats to *E. coli* endotoxemia to cause ARDS. Low-dose ibuprofen (3.75 mg/kg) enhanced the inflammatory response, while high doses (30 mg/kg) significantly decreased the intensity of neutrophil alveolitis. Methylprednisolone, 30 mg/kg, had no effect. Harvey et al.[43] used a *Pseudomonas* injection to induce ARDS in pigs. Methylprednisolone significantly improved cardiac index, but other hemodynamic parameters and oxygenation were not improved Ibuprofen, 12.5 mg/kg, given 20 and 120 minutes after bacterial injection, however, significantly improved arterial oxygenation and early pulmonary hypertension and prevented elevations of thromboxane, albumin flux, and extravascular lung water. Traber et al.[44] found a biphasic pulmonary response in sheep to injected endotoxin. Ibuprofen and diphenhydramine eliminated the early response of increased protein-poor lymph flow, increased pulmonary artery pressure, and decreased cardiac index and leukocyte count. The later responses were unaltered.

Smoke injury has been examined in three different animal models. Shinozawa et al.[45] studied synthetic smoke-induced pulmonary edema in rats. Indomethacin blocked increases in thromboxane and in prostacyclin metabolites, while failing to prevent lung edema. Ibuprofen, however, diminished the increase in thromboxane as it augmented the rise in prostacyclin while preventing lung edema. Kimura et al.[46] examined sheep undergoing burning-cotton smoke-inhalation injury. Animals treated with ibuprofen had less severe elevations of lymph flow in the lung than did control animals. Elevated metabolites of arachidonic acid, especially those generated by the cyclooxygenase pathway, are suspected to be part of the mechanism. Pretreating a rabbit model of cigarette smoke lung injury with ibuprofen was found to cause decreased lung compliance, increased pulmonary edema, and frequent death.[47] These results have not been reproduced.

Finally four different models of lung injury have confirmed the pulmonary benefits of ibuprofen. Utsunomiya et al.[48] found that within 30 minutes of acid aspiration, dogs developed pulmonary platelet trapping and platelet release of thromboxane. Within two hours white blood cell entrapment occurs and the release of thromboxane increases. Ibuprofen, given one hour after aspiration, decreased the platelet response, prevented WBC sequestration, and minimized lung edema and inflammation. Perlman[49] used thrombin in sheep to induce pulmonary microemboli. Ibuprofen inhibited the resultant changes. Specifically, ibuprofen reduced pulmonary lymph flow, decreased lymph protein clearance, lessened the change in pulmonary vascular resistance, and returned the neutrophil count to baseline. Meclofenamate, another cyclooxygenase inhibitor, was not effective. Sprague[50] found that ibuprofen, administered to dogs with acute unilateral ethchlorvynol lung injury, caused significant decreases in venous admixture. Furman et al.[51] used oleic acid to cause lung injury in dogs. Ibuprofen improved hypoxemia and lessened the increase in extravascular lung water. This action, however, was mediated by an unknown mechanism, not involving cyclooxygenase.

It is clear that ibuprofen improves pulmonary function under various conditions of acute injury. Primary lung injury and distant insults with secondary pulmonary effects both respond to the drug. The mechanism in some, but not all, cases seems related to cyclooxygenase inhibition. Again the role of superoxide radicals is suggested but has not been examined in detail.

Wound Healing

Ibuprofen also has been shown to improve several aspects of wound healing ranging from wound edema to adhesion formation to vascular obstruction. Suggestions of possible mechanisms are presented.

Alexander et al.[52] found a significant reduction in rat burn wound edema with ibuprofen therapy. Evans blue was injected before burn injury, and ibuprofen was administered 90 minutes after burn. Significantly less extravasation of dye was seen in treated animals. Demling and Lalonde[53] supported this finding in sheep. Second-degree burn wounds treated with topical 5% ibuprofen two and five hours after burn showed significantly reduced lymph drainage and no increase in wound water content. Levels of thromboxane and 6-Keto-$PGF_{1\alpha}$ in lymph fluid were curtailed in treated wounds while systemic prostanoid production was unaffected. Decreased wound edema and decreased production of inflammatory mediators would presumably improve wound healing. In one study of partial-thickness guinea pig burn wounds, however, topical ibuprofen and other nonsteroidal anti-inflammatory drugs did not improve healing as determined by hair growth and restored dermal microcirculation.[54] Other studies are needed to address this point.

The formation of adhesions is an area of concern to all surgeons. The gynecology literature contains reports from several centers showing decreased adhesion formation using ibuprofen. Most studies examined the development of adnexal adhesions. Siegler et al.[55] examined rabbits 2 to 3 weeks after fallopian tube injury. Dexamethasone and ibuprofen were equally effective inhibitors of the formation of significant adhesions. Nishimura's group[56,57] produced uterine horn injuries in rabbits and evaluated the formation of peritoneal adhesions. Ibuprofen inhibited or prevented peritoneal adhesions in a dose-dependent fashion. A positive correlation was found to exist between the formation of glycosaminoglycans and collagen in the healing site and the subsequent formation of adhesions. Suppression of fibroproliferative inflammation occurs.

DeLeon studied the formation of fallopian tube adhesions in guinea pigs and rats. Ibuprofen and indomethacin were equally effective in reducing postoperative adhesions in guinea pigs.[58] Oral and intramuscular ibuprofen each reduced the formation of adhesions in rats. Surprisingly 32% Dextran 70 had no effect alone but acted synergistically with oral ibuprofen and resulted in less formation of adhesions than ibuprofen alone.[59] O'Brien[60] evaluated histologic markers of tissue repair in sheep undergoing adnexal surgery. Vascular ingrowth, fibroblastic proliferation, and mesothelial regeneration were reduced in treated animals. No change was noted in gross adhesion formation, however.

A study of primate extremities showed that oral ibuprofen significantly reduced the force required for tendon gliding after flexor tendon injury in zone II. The breaking strength of completely divided and repaired extensor tendons was unfortunately reduced in treated animals 4 to 6 weeks after injury.[61] The role of ibuprofen in preventing adhesion formation is still being examined. Fibroproliferative antagonism seems to occur. It is hoped that this mechanism will prove to be clinically useful.

Our laboratory has examined the effects of ibuprofen and other nonsteroidal anti-inflammatory drugs on postburn dermal vascular occlusion. The vascular occlusion that normally occurs in burn trauma was prevented in rats by intramuscular ibuprofen or imidazole but not by indomethacin or hydrocortisone. Thromboxane and prostacyclin were not involved.[62,53] Further study of wound fluid collected in subcutaneous chambers revealed a fibrinolysis inhibitor with molecular weight 43,000. The inhibitor was antagonized by ibuprofen in an *in vitro* fibrin plate assay.[64]

Human burn-blister fluid also contained a fibrinolysis inhibitor antagonized by ibuprofen in a dose-dependent fashion. Indomethacin, imidazole, and tolmetin were ineffective in restoring fibrinolysis.[65] The cell of origin of fibrinolysis inhibitor appears to be the dermal endothelial cell (EC). ECs in culture produce a fibrinolysis inhibitor that is also antagonized by ibuprofen but not by indomethacin, imidazole, or tolmetin.[66] Increased postburn vascular patency should prevent secondary necrosis in the zone of stasis and should reduce the incidence of morbidity.

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Postoperative Myocardial Infarction and Cardiac Death

Predictive Value of Dipyridamole-Thallium Imaging and Five Clinical Scoring Systems Based on Multifactorial Analysis

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Sixty-six patients unable to complete a standard preoperative exercise test because of physical limitations were studied to determine the predictive value of individual clinical parameters, of clinical scoring systems based on multifactorial analysis, and of dipyridamole-thallium imaging before major general and vascular surgery. Study endpoints were limited to postoperative myocardial infarction or cardiac death before hospital discharge. There were nine postoperative cardiac events (seven deaths and two nonfatal infarctions). There was no statistical correlation between cardiac events and preoperative clinical descriptors, including individual clinical parameters, the Dripps-American Surgical Association score, the Goldman Cardiac Risk Index score, the Detsky Modified Cardiac Risk Index score, Eagle's clinical markers of low surgical risk, and the probability of postoperative events as determined by Cooperman's equation. There were no cardiac events in 30 patients with normal dipyridamole-thallium scans or in nine patients with fixed myocardial perfusion defects. Of 21 patients with reversible perfusion defects who underwent surgery, nine had a postoperative cardiac event (sensitivity, 100%; specificity, 43%). In the six other patients with reversible defects, preoperative angiography showed severe coronary disease or cardiomyopathy. Thus in patients unable to complete a standard exercise stress test, postoperative outcome cannot be predicted clinically before major general and vascular surgery, whereas dipyridamole-thallium imaging successfully identified all patients who sustained a postoperative cardiac event.

CARDIAC COMPLICATIONS are a major cause of postoperative morbidity and death after vascular and major general surgery when there is coexisting coronary artery disease.[1-3] Available methods used to identify high-risk coronary patients include clinical history and physical examination, resting electrocardiography, clinical scoring systems, exercise testing, dipyridamole-thallium imaging, and systematic coronary angiography. The latter is not practical as a screening procedure. Most authors agree that if the exercise stress test is clinically and electrically negative at 85% of the maximal predicted heart rate, a patient can safely undergo surgery.[4-6] Unfortunately many patients cannot achieve an adequate exercise level because of peripheral vascular disease, advanced age, neurologic or locomotor problems, or beta blocker use. The present study was undertaken to assess the predictive value of individual clinical parameters, of five clinical scoring systems, and of dipyridamole-thallium imaging for postoperative cardiac events in patients with suspected or known coronary artery disease unable to achieve an adequate level of exercise on the treadmill.

Material and Methods

Patient Population

The study population consisted of 66 consecutive patients referred for dipyridamole-thallium imaging before major general or vascular surgery. Reasons for referral for cardiac risk assessment included multiple risk factors, a history of atypical chest pain, resting electrocardiographic abnormalities, or suspected or known coronary artery disease. An adequate level of stress on the standard treadmill test could not be achieved either because of physical limitations or because of beta blocker use.

Clinical Evaluation

Medical charts were reviewed and Dripps-American Surgical Association score,[7] Goldman Cardiac Risk Index score and class,[8] Detsky Modified Risk Index score and class,[9] Eagle's criteria,[10] and Cooperman event

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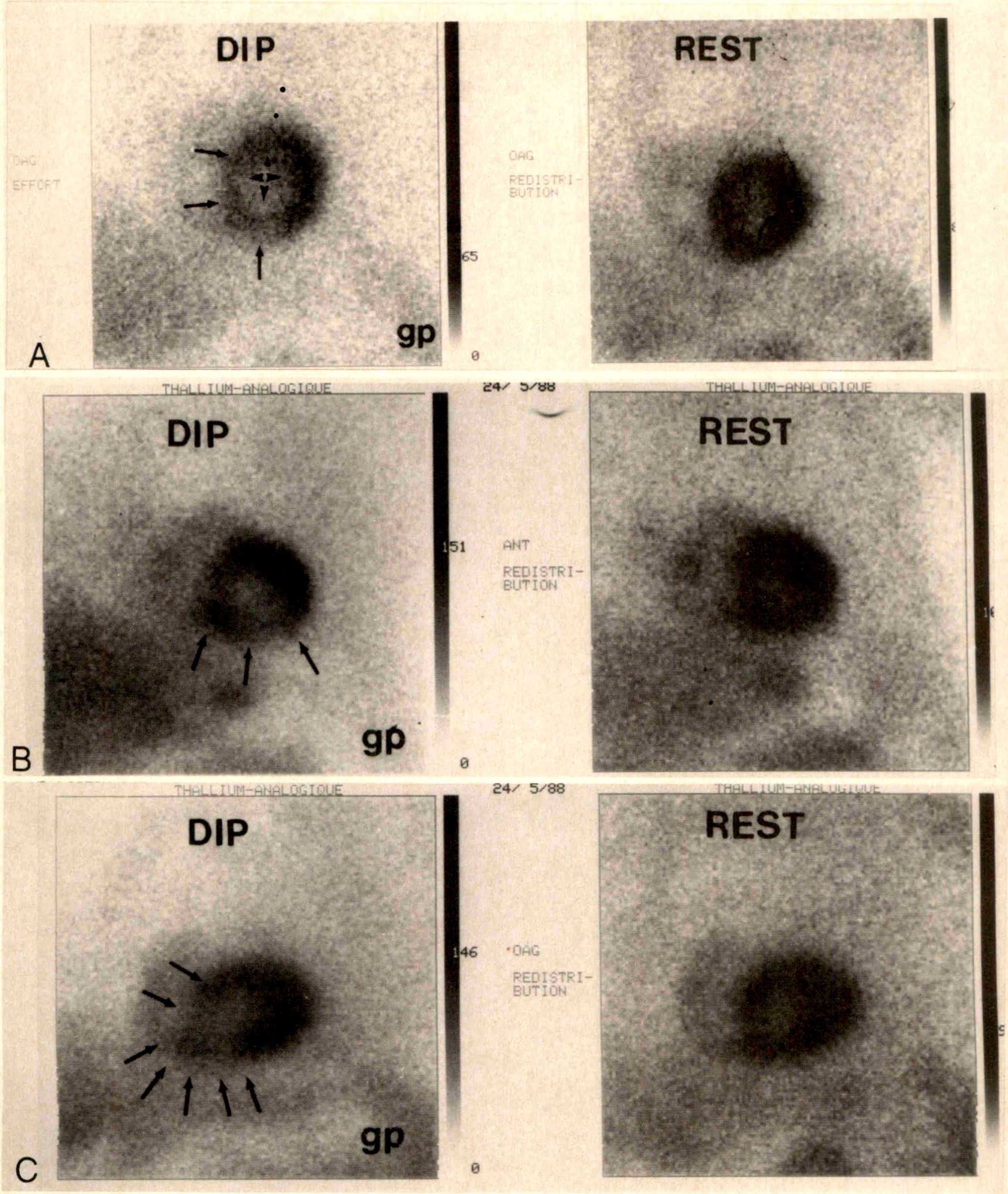

FIGS. 1A–C. Fifty-seven-year-old man admitted for surgery of the right superficial femoral and popliteal arteries. He had had a remote myocardial infarction, but denied any angina. Immediate postdipyridamole (left) and redistribution (right) thallium myocardial perfusion images in the best septal (A), left anterior 70 degree (B), and anterior (C) views show severe, completely reversible perfusion defects of the septal, inferoapical (A), anterior, apical, and inferior (B and C) myocardial segments. Peri- and postoperative outcome was uneventful until he died suddenly six days after surgery.

probability[11] were determined for each patient. The scoring systems are described in Table 1. As described in Table 2, 48 patients underwent major reconstructive vascular surgery and 18 underwent major general surgery.

Dipyridamole Infusion Protocol

The dipyridamole infusion protocol was described in detail in a previous report.[12] Briefly, patients were studied in the fasting state, having avoided coffee, tea, soft drinks, and chocolate for 24 hours, and all theophylline derivatives were discontinued for 48 hours before the test. A 20-gauge canula was installed in a large antecubital vein and the cardiac rhythm was continuously monitored with a II lead. Baseline and q 1 mn heart rate and blood pressure were recorded. Dipyridamole was infused at a rate of 0.14 mg/kg/minute over four minutes. After the infusion, the patient stood up and walked in place for two minutes. At that point, 3 mCi of thallium-201 was injected as a compact bolus into the canula, which was rapidly followed by a 10-mL bolus of normal saline solution. The patient continued walking on the spot for two minutes and then imaging was begun under the scintillation camera. During each study aminophylline 125 mg was available to reverse any serious adverse effects of dipyridamole. There were no major irreversible side effects from dipyridamole in the 66 patients. Patients who developed symptomatic myocardial ischemia responded quickly to intravenous aminophylline. The mean variation in heart rate and systolic blood pressure after dipyridamole infusion were, respectively, 9.1 ± 8 beats per minute and 17 ± 19.8 mm Hg.

Thallium-201 Myocardial Imaging

The first image was taken in the best septal view, followed by the left anterior oblique 70-degree (with manual breast support by the technician in female patients) and

TABLE 1. *Clinical Scoring Systems*

Test	No. of Patients
Goldman Cardiac Operative Risk Index[8]	
History	
Age > 70	5
Myocardial infarction < 6 months	10
Aortic stenosis	3
Physical exam (third heart sound, S3 gallop, or signs of congestive heart failure)	11
Electrocardiogram	
Any rhythm other than sinus	7
> 5 premature ventricular contractions/mn	7
Poor general medical condition	3
$PO_2 < 60$	
$P\,CO_2 > 50$	
$K^+ < 3$	
BUN > 50	
Creatinine > 3 (>260 mmol/L)	
Bedridden	
Operation	
Emergency	4
Intrathoracic or intra-abdominal or aortic	3
Total points = 0 to 53	

Goldman Classification	Total points
1	0–5
2	6–12
3	13–25
4	>25

Test	No. of Patients
Detsky Modified Multifactorial Risk Index[9]	
Coronary artery disease	
Myocardial infarction within 6 months	10
Myocardial infarction more than 6 months	5
Canadian Cardiovascular Society angina	
Class III	10
Class IV	20
Unstable angina within 6 months	10
Alveolar pulmonary edema	
Within 1 week	10
Ever	5
Valvular disease	
Suspected critical aortic stenosis	20
Arrhythmias	
Rhythm other than sinus (may have APB's)	5
More than 5 PVC's prior to surgery	5
Poor general medical status	5
Age over 70 years	5
Emergency operation	10
Total score: 0 to 120	

Detsky Classification

Detsky class	Total points
1	0–15
2	16–30
3	>30

Eagle Vascular Surgery Low Risk Clinical Markers[10]

The patient is considered to be at low risk for surgery if the following 5 clinical markers are absent: history of angina, clinical or electrocardiographic evidence of prior myocardial infarction, diabetes and congestive heart failure.

Cooperman equation[11]

$$P = \text{antilog}_2[(C_1 * X_1) + (C_2 * X_2) + \cdots + C]$$

X_1 = angina ($C_1 = 0.46$)

X_2 = congestive heart failure ($C_2 = 1.02$)

X_3 = arrhythmia ($C_3 = 0.62$)

X_4 = previous myocardial infarction ($C_4 = 0.64$)

X_5 = cerebrovascular accident ($C_5 = 1.15$)

X_6 = abnormal electrocardiogram ($C_6 = 1.25$)

Dripps-American Surgical Association Physical Status Score[7]

1 = normal healthy patient for elective operation
2 = mild systemic disease
3 = severe systemic disease with limited activity but not incapacitated
4 = incapacitating systemic disease which is a constant threat to life
5 = moribund patient not expected to survive 24 hours with or without operation

TABLE 2. *Surgical Procedures*

Procedure	No. of Patients
Vascular surgery (n = 48)	
Limb vascular procedures	12
Aortomesenteric bypass	1
Aortorenal bypass	4
Elective aortic replacement for aortoiliac arteriosclerotic disease	16
Elective resection of abdominal aortic aneurysms	11
Carotid endarterectomy	4
Major general surgery (n = 18)	
Hysterectomy	4
Hemicolectomy for colonic cancer	2
Renal transplant	1
Marshall-Marchetti	1
Radical cystectomy	1
Radical thyroidectomy	2
Total hip prosthesis	3
Excision of infected prosthesis	1
Ankle reconstruction	1
Gastrectomy	2

anterior views. Delayed images were obtained four hours after thallium injection and the patient was instructed to eat lightly during that time interval. Preset time eight-minute images were taken in each of the three views (initial and delayed images) with a photopeak set at 80 kev with a 20% window. Care was taken to position the patients identically for the initial and redistribution studies. For each scintigraphic study, the following images were displayed: analog images, interpolated background subtracted images, circumferential profiles, and washout rate analysis. All myocardial scintigraphic images were interpreted by two experienced observers without prior knowledge of patient history, coronary anatomy, or postoperative outcome. The myocardium was divided into three segments in each view for a total of nine segments. Scans were interpreted either as normal, as showing a fixed defect, or as displaying a reversible defect in at least one myocardial segment.

A fixed defect was defined as an initial perfusion defect with no redistribution on delayed images, plus electrocardiographic evidence of a necrosis in the corresponding segment with a clinical history of myocardial infarction and documented elevation of cardiac enzymes (when available) proportional to the size of the observed perfusion defect. Otherwise, because of the high reported incidence of viable but stunned myocardium in fixed defects,[13] we took either delayed 24-hour resting thallium images or a radionuclide gated equilibrium ventriculogram (MUGA scan) under continuous intravenous nitroglycerin infusion to confirm the presence of scar tissue. Infrequent differences in interpretation were resolved by consensus.

Study Endpoints

Only cardiac death (acute myocardial infarction or sudden unexpected death) and acute myocardial infarction before hospital discharge were accepted as endpoints. Acute myocardial infarction was diagnosed when at least two of the following three criteria were met: (1) a recent episode of characteristic chest pain that lasted more than 30 minutes; (2) a transient increase above the upper limit of normal of total serum creatinine kinase (CK) and its myocardial isoenzyme subfraction (MB CK), related temporally to the episode of chest pain; and (3) Minnesota code criteria for definite or probable myocardial infarction accompanied by evolving ST- and T-wave changes.[14,15] The results of thallium studies were made available to referring physicians who decided to refer the patient either for coronary angiography or directly to surgery. Sixty patients went to surgery, with antianginal drug therapy when there was thallium redistribution. The choice of drug therapy was not standardized and depended on the preferences of the referring physician. Patients with redistribution were usually monitored with a Swan-Ganz catheter during surgery, transferred to the intensive care unit after operation, and followed by the consulting cardiologist after operation.

Statistical Analysis

Correlation between clinical parameters, scoring systems, results of dipyridamole-thallium imaging, and cardiac events was done using chi square and ANOVA analysis. All values are mean ± standard deviation.

Results

Clinical Features and Postoperative Outcome

The clinical features of the 66 patients are listed in Table 3. No patient had preoperative clinical evidence of heart failure. Among the 60 patients who underwent surgery, 51 had an uneventful outcome, and 9 had cardiac events: 7 cardiac deaths (6 due to myocardial infarctions and 1 sudden death) (Fig. 1) and 2 nonfatal myocardial infarctions. The latter two infarctions included one transmural anterior infarct, and one non-Q wave infarct. Cardiac events appeared two to six days after operation (mean, 3.9 days). Surgery was cancelled in six of the patients who had thallium redistribution; all underwent preoperative coronary angiography and either had significant coronary artery disease (five) or cardiomyopathy (one), as illustrated in Table 4.

Predictive Value of Clinical Parameters

There was no statistical correlation between either individual clinical parameters (Table 3) or the scoring sys-

TABLE 3. *Clinical Predictors*

Clinical Parameter n = 66	No Event 51 pts. (%)	Event 9 pts (%)	Surgery Cancelled 6 pts (%)
Age	58.3 ± 10.7	63.1 ± 6.7	57.5 ± 9.32
Number of men	26 (51)	6 (66)	2 (33)
Surgery			
Vascular	42 (82)	6 (66)	3 (50)
Abdominal procedure	34 (66)	5 (55)	4 (66)
Cerebrovascular disease	10 (19)	3 (33)	2 (33)
COPD	11 (21)	3 (33)	1 (16)
Cr > 260 mmol/L	4 (7)	0	1 (16)
Risk factors			
Mean number	1.63 ± 0.91	1.89 ± 0.99	2 ± 1
Smoking	42 (82)	7 (77)	5 (83)
Hypertension	21 (41)	4 (44)	3 (50)
Diabetes	10 (19)	4 (44)	2 (33)
Family history	8 (15)	0	1 (16)
Angina grade			
0	24 (48)	7 (77)	5 (83)
1	1 (2)	0	0
2	12 (23)	1 (11)	1 (26)
3	1 (2)	0	0
Atypical chest pain	12 (23)	1 (11)	0
Previous MI	13 (25)	5 (55)	0
Electrocardiogram			
LVH	7 (13)	4 (44)	1 (16)
ST-T	16 (31)	4 (44)	4 (66)
Arrhythmia	5 (9)	4 (44)	0

COPD, chronic obstructive pulmonary disease.
Cr, creatinine.
Angina grade, Canadian Classification.
Previous MI, previous myocardial infarction.
Electrocardiogram, LVH: left ventricular hypertrophy.
ST-T, ST-T segment anomalies.
Arrhythmia, any rhythm other than sinus or more than five premature ventricular contractions per minute.
Abdominal procedure, intra-abdominal procedure.

tems (Table 5), and postoperative outcome, with one exception. The relation between the Cooperman probability of a cardiac event and postoperative outcome attained borderline statistical significance ($p = 0.05$), but there is a wide dispersion of individual probability values in each group. For example, although all patients who sustained a postoperative cardiac event had a Cooperman probability greater than 15%, so did 60% (30 of 51) of patients with an uneventful outcome.

Predictive Value of Dipyridamole-Thallium Imaging

No events occurred in the 30 patients with normal scans or in the nine patients with fixed defects as defined in this study. One patient had a fixed anterior wall defect and a history of infarction, but only inverted T waves in the anterior leads on the electrocardiogram. A MUGA scan during continuous nitroglycerin infusion showed normal anterior wall motion. Therefore the anterior wall defect was considered to be completely reversible and the patient was not classified in the fixed defect category. He died three days after operation of an acute myocardial infarction. Twenty-one patients displayed a reversible defect, including the nine patients who sustained a postoperative cardiac event (sensitivity, 100%; specificity, 43%).

Discussion

Failure of Clinical Scoring Systems

No clinical descriptor, including individual clinical parameters and the five scoring systems, could predict postoperative outcome. The absence of a preoperative history of angina in most (78%) patients who sustained a cardiac event underscores the difficulty of evaluating patients who spontaneously restrict their activities in response to peripheral vascular or other limiting diseases.[16]

The poor predictive value of chest pain has been previously reported in a series of 12,654 patients.[1] The Dripps-American Surgical Association classification, although involving the study of 33,224 patients,[7] is more a physical fitness scale than an assessment of peri- and postoperative risk. This probably accounts for its lack of predictive value. The Goldman Cardiac Risk Index,[8] based on the preoperative assessment of 1001 consecutive patients, is straightforward and readily adopted by clinicians but was not separately verified on a hypothesis-testing group of patients in the original study. It later yielded less encouraging results in a validating set of patients.[9] Detsky developed a modified version of the Goldman multifactorial scoring system that was validated on a group of 455 patients.[9] In our study all patients who developed postoperative cardiac events were classified at relative low risk (class 1 or 2) according to Detsky's scale.

In a series of 111 patients, Eagle observed that there were no cardiac events in patients with no angina, congestive heart failure, diabetes, previous myocardial infarction, or electrocardiographic Q waves.[10] In our study one third of patients with a cardiac event would have been classified as low risk according to Eagle's criteria. Determination of event probability from Cooperman's equation,[11] developed by multivariate analysis in 566 patients, showed

TABLE 4. *Angiographic Data of Patients Whose Surgery Was Cancelled*

Patient	LM	RCA	LAD	Cx	Procedure Cancelled
1	75	0	0	0	Elective aortic replacement
2	50	50	100	100	Elective resection of AAA*
3	0	100	80	75	Thyroidectomy
4	0	100	70	0	Ankle reconstruction
5	0	50	85	50	Aorto-renal bypass
6 cardiomyopathy: EF = 34%					Renal transplantation

* AAA, abdominal aortic aneurysm.
EF, ejection fraction.
LM, RCA, LAD, and Cx, Left main, right, left anterior descending and circumflex coronary arteries.
All patients had thallium redistribution.

TABLE 5. *Failure of Clinical Scoring Systems to Predict Postoperative Events*

Scoring System (n = 66)	No Event 51 pts (%)	Event 9 pts (%)	Surgery Cancelled 6 pts (%)	p
Dripps-ASA				
Total score	2.14 ± 0.99	2.22 ± 0.42	2 ± 0	NS*
Goldman				
Total score	4.36 ± 3.36	3.67 ± 4.42	3.33 ± 2.92	NS
Number of patients in low risk class 1 or 2	50 (98)	8 (89)	6 (100)	NS
Detsky				
Total score	4.51 ± 5.71	5 ± 3.33	4.67 ± 2.98	NS
Eagle criteria				
Number of pts. classified at low risk	14 (27)	3 (33)	2 (17)	NS
Cooperman equation				
Probability (%)	21 ± 17	37 ± 24	31 ± 27	0.05

See Table 1 for description of scoring systems.

* Not significant.

a weak statistical correlation ($p = 0.05$) with postoperative outcome. Furthermore the range of probabilities in both groups is so wide that prediction of postoperative outcome is not feasible in individual patients. Cooperman realized this problem and urges that caution must be used in applying the risk equation to individual patients.[11]

Clinical Significance of Silent Myocardial Ischemia

Silent myocardial ischemia is now well recognized as being as important as symptomatic ischemia in the evaluation of whether a coronary patient is at risk for myocardial infarction or sudden death.[17–21] For example data on 424 patients from the Coronary Artery Surgery Study (CASS) Registry shows that patients with exercise-induced angina or silent ischemia have a similar risk of developing an acute myocardial infarction or sudden coronary death, except in patients with three-vessel coronary artery disease in which the risk is greater in asymptomatic patients.[17]

With respect to preoperative cardiac assessment, this may explain the failure of all clinical modalities that rely on symptomatic ischemia as a risk indicator, such as a history of angina, the Eagle clinical markers, the Detsky Modified Cardiac Risk Index, and Cooperman's equation. Thallium imaging has the advantage of being a very sensitive tool to detect both symptomatic and silent ischemia,[22] and has been shown to be more sensitive than the exercise electrocardiogram.[23]

Dipyridamole-Thallium Myocardial Perfusion Imaging

The poor predictive value of clinical descriptors leaves only exercise testing and dipyridamole-thallium imaging as practical noninvasive means of identifying high risk patients. Exercise testing is frequently nondiagnostic in patients with peripheral vascular disease, advanced age, neurologic or locomotor problems, or beta blocker use,[24] and should probably be avoided in patients with a large abdominal aortic aneurysm because of the low risk of rupture.[25] Thallium imaging after dipyridamole-induced coronary vasodilation produces myocardial perfusion images similar to those obtained after exercise and have been shown to be as sensitive and specific as thallium exercise testing for the diagnosis of coronary artery disease.[26,27]

In our study, all 39 patients with normal dipyridamole-thallium scans or fixed perfusion defects (scar tissue from a previous myocardial infarction) underwent surgery uneventfully, whereas 43% of patients (9 of 21) with thallium redistribution sustained a postoperative cardiac event. Surgery was cancelled in six patients with extensive thallium redistribution on myocardial perfusion images and all had either severe coronary artery disease or cardiomyopathy on coronary angiography. Data compiled from six previous studies[10,28–32] yields results similar to ours: a 1.1% (3 of 272 patients) overall event rate in patients without redistribution and a 29.4% (47 of 160 patients; range, 19% to 43%) event rate in patients with reversible defects.

Management of Patients with Reversible Defects

The management of patients with reversible defects is still controversial. Current recommendations include preoperative coronary angiography with revascularization of high-risk lesions, surgery with antianginal medication, and cancellation or modification of surgery when feasible.[4,5,10,28–33] At the present time, we believe that cases must be managed on an individual basis in the absence of data on the combined morbidity and mortality risks associated with coronary angiography and myocardial revascularization followed by peripheral vascular reconstruction in a population of patients with multi-level vascular disease. Surgeons frequently resort to less aggressive extra-abdominal vascular procedures in high-risk patients in the hope of reducing cardiac risk, whereas there appears to be little or no decrease in cardiac risk by resorting to extra-abdominal vascular reconstruction.[33,34]

Limitations of the Study

The poor predictive value of the multifactorial scoring systems may be related to our choice of study endpoints: only cardiac death and infarction were accepted as postoperative events because these events are irreversible and severe enough to justify preoperative coronary angiography and revascularization. Event rates in our study would have been different had we also chosen unstable angina, pulmonary edema, cardiac arrhythmia, and peripheral emboli as study endpoints. The high ratio of cardiac deaths and transmural infarctions to non-Q wave infarctions in our study may be due either to statistical sampling in a small group of patients who sustained a cardiac event or to the cardioprotective effect of antianginal medication given to patients with thallium redistribution.

Postoperative outcome cannot be predicted by either individual clinical parameters or the five clinical scoring systems studied. However dipyridamole-thallium imaging successfully identified all patients who sustained a postoperative cardiac event.

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Mont R. Reid, M.D. (1889–1943)

A Centennial Tribute

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THE YEAR 1989 marks a double anniversary for The Johns Hopkins Hospital. It is the 100th anniversary of the opening of The Johns Hopkins Hospital as well as the 100th anniversary of the birth of one of its most famous graduates, Dr. Mont Rogers Reid. After graduation from The Johns Hopkins School of Medicine in 1912, Mont Reid progressed to become the 16th resident surgeon trained by Dr. William Stewart Halsted at The Johns Hopkins Hospital, serving in that capacity from 1918 to 1921. He moved to the University of Cincinnati with Dr. George J. Heuer in 1922 to serve as his associate. In 1931 he became the second Christian R. Holmes Professor and Chairman of the Department of Surgery at the University of Cincinnati when Dr. Heuer left for Cornell University. Under his leadership, the Department of Surgery at Cincinnati became known throughout the country as one of the outstanding clinics in graduate surgical education. In 1939 he was offered the Surgical Chairmanship at The Johns Hopkins Hospital, a position he declined because of his dedication to Cincinnati, its medical school, and the school of surgery that he had developed there. His premature death in 1943 was a great loss to the medical and general communities and the flag on the City Hall of Cincinnati was flown at half mast. It is our purpose to honor Dr. Reid for his outstanding personal and professional contributions to surgery, on this, the centennial of his birth (Fig. 1).

The Early Years

Mont Rogers Reid was born on April 7, 1989 in Oriskany, Virginia, a tiny village in the Shenandoah mountains. He was the third youngest in a family of eight children and received his early education primarily from his father until his premature death when Mont Reid was only 9 years old.[1] Reid and his brothers alternated working and going to school on a yearly basis so that they could all attain an education. This strategy was successful because of the eight children in the Reid family, 1 died in infancy, 3 became lawyers, 1 a banker, 1 an engineer, and the only daughter married Dr. George Heuer. Reid became the only doctor in the family. His first formal education was at a Dunkard School in the Virginia mountains. On one occasion, one of Mont Reid's brothers met some mountaineers and became intoxicated with mountain whiskey. When he returned to school he was summoned before the faculty for expulsion. Mont Reid wisely advised his brother to apply immediately for conversion to the Dunkard faith. By doing so his brother was promptly dunked, and his education was preserved.[2] This early episode revealed both the wisdom and pragmatism that characterized Dr. Reid's career.

Later Reid attended the Danville Normal School for 2 years, then entered Roanoke College at the age of 14 years and graduated with an AB degree in 1908. During his last 2 years in college, Reid and an older brother took the competitive examinations for both the Rhodes Scholarship and a Johns Hopkins University Scholarship. The older brother won the Rhodes Scholarship by one point with Mont finishing second; Mont won the scholarship to Johns Hopkins and decided to study medicine. Because his family's financial resources were inadequate for his support, the farmers in the village of Oriskany loaned Mont the necessary money to enable him to enter medical school. He demonstrated his maturity and appreciation by immediately purchasing a life insurance policy for $3000 to guarantee the repayment of the loan in the event of his death.[2] Because of his brilliant record in medical

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FIG. 1. Mont R. Reid, M.D., 1889–1943.

school, he was offered an appointment as a surgical intern at The John Hopkins Hospital in 1912 by Dr. William Stewart Halsted. This was the beginning of an association with Dr. Halsted that lasted 10 years.

The Hopkins Years

After 1 year of surgical internship, Reid became the assistant resident of pathology, after which he returned to surgery and held the position of assistant resident surgeon from 1914 to 1918. Halsted had originally planned to allow Reid to leave the Hopkins Surgical Service without first becoming the Chief Resident, and in fact had appointed Ernest G. Grey to that position. Dr. Grey kindly offered to postpone his appointment for 6 months to give Dr. Reid an opportunity to be the chief resident. Tragically Grey subsequently died in the great influenza epidemic, allowing Reid to occupy the prestigious post of resident surgeon from 1918 to 1921.[1] Immediately after his surgical residency, Reid served for 2 months as the personal physician to a wealthy man with an elaborate estate at Jeckyl Island, Georgia. This was a difficult social experience. Reid later confessed that he had no idea which of the numerous knives or forks to select for the various courses of the long formal dinners at the estate. The other employees were equally unfamiliar and of no help. Thus the young Dr. Reid was too embarrassed to help himself to many of the various dishes that were offered to him. He never forgot this unpleasant experience. This perhaps explains his extraordinary efforts to make young men feel completely at ease when he was their host.[2]

In 1921 Reid was appointed an associate surgeon to The Johns Hopkins Hospital. During his 10-year period of association with Halsted, he mastered the gentle, meticulous techniques that Halsted had introduced into surgery. Reid also developed a keen interest in the principles of wound healing, became fascinated with the surgery of blood vessels, and acquired extraordinary clinical and diagnostic abilities. Reid's enormous capacity for sound judgment, diagnosis, and treatment were partly due to the nearly father-to-son relationship between the austere perfectionist Halsted and his pupil (Fig. 2). On one occasion

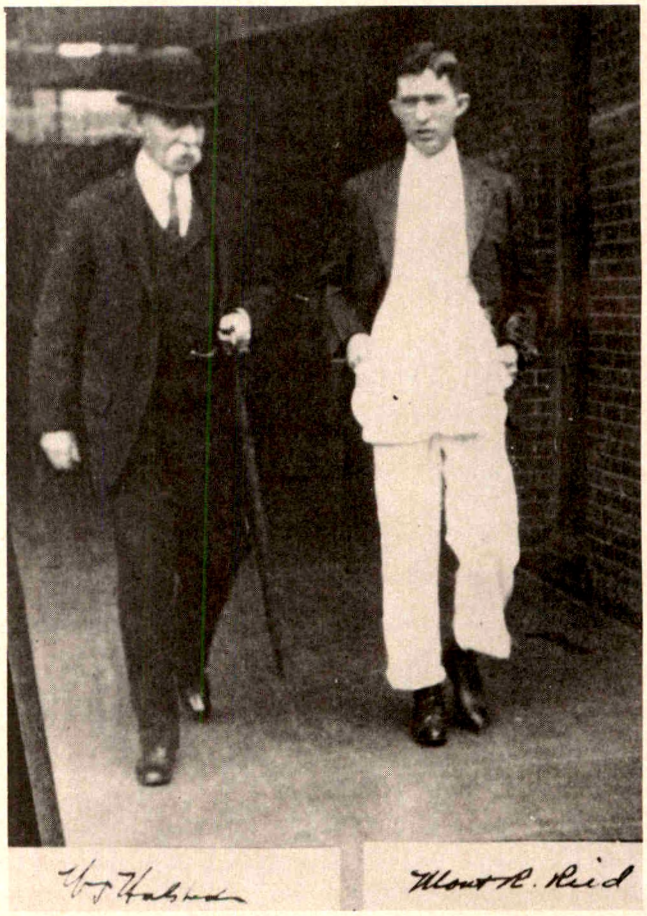

FIG. 2. Mont Reid (right) with Dr. Halsted at The Johns Hopkins Hospital.

Halsted told Reid how unfortunate it was that a patient whom they were examining had such severe heart disease, because surgical cure of the patient's large arteriovenous fistula was prohibited because of the operative risks. This comment stimulated an experimental study in the Hunterian Experimental Laboratory. Reid reasoned that the diversion of blood from artery to vein might increase the work of the heart; therefore the coexistence of an arteriovenous fistula and heart disease may be more than coincidence. In the Hunterian Laboratory he created experimental arteriovenous fistulas in animals.[3] By the end of 1 year he had shown that all of the animals had developed marked cardiac enlargement or frank congestive heart failure. Halsted, who not only had affection but also vicarious pride in Reid's surgical accomplishments, was delighted and soon patients were successfully treated for both aneurysms and heart disease by ligation of such fistulous communications.[4,5] In 1922 Reid accompanied Dr. George Heuer to Cincinnati as his associate and right-hand man in the newly organized Department of Surgery at the University of Cincinnati Medical College. This was a period of great change with all the difficulties inherent in such a transition. Dr. Heuer later said that Reid's "loyalty, sound judgment, and winning personality contributed greatly to such success as was achieved in the development of the Department of Surgery."[2]

Dr. Reid and Dr. Halsted shared a strong mutual affection that did not suffer when Reid left Johns Hopkins. They remained in close contact by mail and visited Halsted's summer home at High Hampton, North Carolina. In a letter dated May 21, 1922, Reid wrote to Halsted about his early impressions of Cincinnati:

> I meant long ago to write you and say if nothing more, how sorry I was to leave Baltimore without seeing you. Even at this late date I am not sure that my opinions about Cincinnati and its University are sufficiently stabilized to permit me to express them in writing. However, I know that I can safely say anything to you . . . realizing that in a few more months I may feel entirely differently. I know that I am receiving an invaluable experience and am thoroughly enjoying it. I am not, however, so certain about the ultimate result of our efforts. The evils of the place, as I see them, are going to be awfully hard to overcome. Everywhere among students, teachers, and interns there is a time consuming disposition toward intimate fellowship. Throughout the day you can see groups of interns or students about an "attending" or "professor" who is amusing them with smutty jokes or otherwise obviously courting them for the sole purpose of securing their practice. The type of individual met amusing the doctors is far from that I have been accustomed to at Hopkins. Their ideals are different; they do not study; their efforts tend to foster a form rather than a good model. These are big hampering factors in the development of the institution . . . During the past month I have completely reorganized the plan of teaching the third and fourth year students. The main departments of these two years are so strongly behind our place that I believe the committee on curriculum will adopt it without any changes . . .
>
> My other main interest has been in planning for the department of surgical pathology . . . The next big problem will be our effort to improve the nursing situation. Between the doctors and officials of the hospital, and the officials of the training school there is a tremendous amount of ill feeling, and as a result there is not much cooperation. I am going to try in some way to improve this situation though I am not very optimistic of accomplishing a great deal of good . . . My health has steadily improved since I came out here. The almost complete relief from the cutting pains in my chest that have bothered me for the last four years, and the gradual recovery from the sleeplessness and unhappy state of mind that harassed me during the last year in Baltimore have more than justified the change. These benefits, together with the invaluable experience in reorganization and diplomacy will, I think, not permit me to regret leaving Baltimore.

It was Reid and Heuer who were summoned urgently to Baltimore when Halsted was hospitalized for cholangitis. Despite their successful removal of Halsted's common duct stones, his condition worsened and he died on September 7, 1922.[6]

The Cincinnati Years

After 3 years in Cincinnati, Reid was appointed the Visiting Professor to the Peking Union Memorial College of China in 1925. He was charged with running a large base hospital that saw active service in the civil war then dividing China. During his year in China, Reid made many friends among the Chinese people, from whom he continued to receive letters, presents, and visits throughout his life. As surgeon to the Roy Chapman Andrews Expedition into Mongolia in 1926, Dr. Reid was awarded a medal for his services with Ling Yu Sheng's Chinese army. He returned to the United States in 1926 after traveling through the Mayla Peninsula where he contracted malaria that, for a time, impaired his health.[1] In 1926 Reid resumed his position as Associate Professor of Surgery at the University of Cincinnati and simultaneously became active and successful in private practice.

In 1929 Reid married Elizabeth Cassatt and on their wedding trip they attended the International Surgical Congress in Warsaw, Poland. Mrs. Reid was soon introduced to the Halstedian tradition of gentle handling of tissues, for her distinguished husband developed a small carbuncle behind his ear that he could not see. He insisted that his bride dress and care for the lesion, refusing to consult an Austrian physician with the remark that "all good Viennese doctors are pathologists, and I won't let one touch me."[2] One son resulted from their marriage. Reid also soon acquired two hobbies, sailing and golf, which became his principle forms of relaxation.

In 1931, with George Heuer's departure to head the Surgery Department at Cornell University in New York, Reid was appointed Christian R. Holmes Professor of Surgery and Director of the Surgical Services at Cincinnati General Hospital. As professor of surgery he assumed his responsibilities in a serious and energetic manner and worked diligently to involve the community in the medical school.[2] Extra offices and laboratories were established and new fellowships were created for young physicians interested in surgical research. Dr. Reid then initiated improvements in the residency system of surgical training, a method begun in Germany and further developed by Halsted in this country.[6] This method of prolonged postgraduate training began with the appointment by Reid of a capable intern as an assistant resident in the graduate school of surgery for a 1-year period. If successful in the fierce competition that ensued, the young surgeon continued to receive yearly appointments in various subspecialties of surgery such as gynecology, orthopedics, and surgical pathology. After 6 to 7 years the most outstanding surgeon from an initial group of 12 would be appointed Chief Resident for 1 year. During this year the resident was responsible for the care of all patients on the surgical service of the Cincinnati General Hospital. This magnificent opportunity for advanced and prolonged training attracted young men of the highest caliber from all parts of the United States and soon hundreds of applications for appointments to Reid's service were arriving every year.[2] As a teacher Reid was not a brilliant lecturer nor an inspiring master of the clinical method of instruction. However at the bedside his kindness to patients, his attention to the salient facts of the history, his careful physical examination, his critical interpretation of clinical data, his sound techniques in the operating room, and his good medical judgment were great examples to both undergraduate and advanced students.[1]

Several interesting incidents occurred at this period of Dr. Reid's career that illustrate certain aspects of his character. A young surgical resident returned from his wedding trip with his wife, a yellow convertible, and 50 cents. Nervously he called Reid at his home to ask for a loan of $50. Reid went to his desk, wrote out a check for $2500, and remarked "I want you to concentrate on surgery and not be worried about money; pay me back whenever you find it convenient and for heaven's sake next time buy a black car!"[2] Another example of Reid's generosity is exemplified by the case of a young woman from his home town of Oriskany, Virginia, who developed a life-threatening soft-tissue infection of her hip. She was sent to Reid for examination. Realizing that hospitalization was necessary, he arranged her admission. About this time the young woman's father became bankrupt. The infection was stubborn and resisted all forms of treatment. Reid insisted that she remain in the hospital for more than a year, and during this period he paid all the hospital bills out of his own pocket. Finally she recovered completely.[2]

In the years from 1931 to the time of his death, Reid's surgical career was notable primarily because of his astonishing diagnostic ability and superb judgment. His memory of other patients with similar conditions was uncanny and his ability to profit from experience was unique. Regularly on Wednesday mornings in a dreary, poorly lit room in the basement of the Cincinnati General Hospital, the most complicated diagnostic cases from the large outpatient departments and wards of the hospital were assembled by the resident staff for discussion. All the community surgeons were invited to this meeting and the large room was usually packed to capacity with visitors, residents, and the senior staff from the Surgical Department. In this type of discussion, Reid's genius as a clinician was apparent to all. Time after time after prolonged discussion and frequent disagreement, Reid would quietly express his opinion, which would subsequently be proved correct at the operating table.

Despite his heavy clinical and administrative responsibilities, Reid still spent much of his time in the animal laboratory studying the effects on the heart and circulation of artificially produced communications between arteries and veins. These important studies were published in significant medical journals and have remained classics in their field.[4,5] The method of quadruple ligation for the care of such lesions as originally advocated by Reid was the basis for the successful treatment of more than 400 patients with such arteriovenous fistulas produced by gunshot wounds in World War II.[7,8] Reid was also particularly interested in the surgery of the thyroid gland and made important contributions to that subject.[9,10] Like Halsted he was also interested with the fundamental principles of surgery such as wound healing* and control of infection.[11,12]

Dr. Reid's reputation as a surgeon among surgeons throughout the United States and abroad was perhaps greater than was generally appreciated in Cincinnati. He was a member of the American Medical Association, American Surgical Association, International Surgical

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*Reid's successor, Josef E. Fischer, the fifth Christian R. Holmes Professor of Surgery, was instructed by one of his great teachers, Robert R. Linton, to read Reid's papers if he wanted to learn about wound healing.

Association, American Association for the Advancement of Science, Society of University Surgeons, National Advisory Cancer Council, Clinical Society of Surgeons, Southern Surgical Association, Central Surgical Association, and the American College of Surgeons. He contributed selflessly to these organizations by serving on various committees and presenting many scientific papers. He was chosen as the first recipient of the Rudolph Matas Medal for Vascular Surgery in 1934 for his work on arteriovenous fistulae. The award, a large gold medallion, was presented in a colorful manner in New Orleans by Dr. Matas himself.[2]

With the death of Dr. Dean Lewis in 1939, Reid was invited to return to Baltimore as Director of Surgical Service of The Johns Hopkins Hospital and Professor of Surgery at The Johns Hopkins University. The decision to accept this great honor was very difficult for Reid. To return to his alma mater as Professor of Surgery and to occupy the most prestigious chair of surgery in the United States was hard to resist. Reid presented to the President of The Johns Hopkins University a series of tradition-shattering requests before he would consider accepting the appointment. Included was a large increase in the budget of the Surgical Department and permission for the Professor of Surgery to have a private practice. To the surprise of nearly everyone, the Board of Trustees in Baltimore agreed to all of his requests.[13] At this juncture a group of Cincinnati businessmen, who were aware of the important contributions that the medical school and Mont Reid were making to Cincinnati, made significant concessions to keep Reid in Cincinnati. Sufficient funds were raised for the Surgical Department of the University of Cincinnati to enable Reid to plan for increasing growth and productivity of his department. This encouraged Reid to remain in Cincinnati, as did his belief that he had begun a job in Cincinnati that was not completed.[1] It has been hypothesized, however, that his life might have been lengthened if he had elected to take an accepted appointment in a fully matured department with adequate financial support.[2] Instead he plunged ahead with long days and nights occupied by administrative duties, teaching, and research projects of the Surgical Department. He also maintained a large private practice in general surgery and was further occupied by advising a host of friends and physicians about their personal problems. Finally Reid made a major effort to interest the community and the City Council in the many problems concerned with the improvement of the medical school and the general hospital. Funds were made available for the construction of a badly needed new building for operating rooms and laboratories. The City Council had decided to name this building, which still stands, the Mont R. Reid pavilion. Reid was also an initial proponent of combining government hospitals with University teaching facilities. His report to the American Surgical Association ultimately led to the founding of the Dean's Committee on Veteran's Hospitals.[14]

Reid was known to his resident staff as Uncle Mont or the Professor. To them he never appeared too busy to hear their troubles and problems. He had a very deep interest in their careers and was anxious and willing to discuss their future plans and to give them sound advice. With his friends he was quiet, unassuming, and invariably friendly and tolerant. With his patients he had an intense personal interest in their comfort and welfare. On entering the room of a postoperative patient, he would frequently rearrange the position of the pillow or their position in bed, attempting to increase the patient's comfort.[2]

Reid spent his vacations with his family in Charlevoix, Michigan, in a cottage of the Chicago Club. There he played golf every morning and became an avid sailor and fisherman. On one occasion a fish hook inadvertently became embedded in Reid's right hand. The fish hook was removed with considerable trepidation by a friend who was greatly surprised to observe the postoperative treatment the distinguished surgeon used on his own right hand. It consisted of prolonged use of soap and water and allowing the hand to trail from the boat in the waters of Lake Michigan for an hour.[2] Antiseptics such as iodine or Mercurochrome were refused because Reid's study of wound healing had convinced him that powerful antiseptics damage injured tissue and allow the growth of bacteria.[15] The wound healed promptly.

In April 1943 Reid suffered a myocardial infarction and during his final illness the extraordinary affection and respect with which he was regarded were exemplified by the numerous inquiries from leaders in the community requesting daily progress reports. Telephone operators, taxi cab drivers, hotel clerks, and newsstand attendants frequently called regarding his condition.[2] Churches offered special prayers for his recovery. At his death on May 11, 1943, the flag of the City Hall of Cincinnati was flown at half mast—a most unusual honor for one not connected with the city government. The American Surgical Association meeting at that time in Cincinnati interrupted its program to attend his funeral.[14] Such honors are a small indication of the remarkable influence the career and character of this great surgeon had on the city of Cincinnati and American surgery.

Perhaps no one has drawn Reid's character as completely yet briefly as an anonymous, grateful patient who wrote: "Nobody but his patients, I believe, could have been aware of his great simplicity, his kindness, and his gentleness of the man himself apart from his skill. He never made brash statements nor raised his voice. If he wasn't sure what was wrong with you he acknowledged it. He had none of the professional bedside manner yet his slow sweet smile inspired hope and faith almost beyond understanding."[2] In the words of George Heuer, "Mont Reid seems particularly to have fitted into his environment, a community of citizens who have an enduring memory for those who serve them well. By them particularly Mont Reid will not soon be forgotten."[2] It is our purpose to honor Dr. Reid for his outstanding personal and professional contributions to surgery, on this, the centennial of his birth.

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Effects of Ischemia and Reperfusion on Protein Synthesis in Livers with Different Glutathione Levels

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The role of oxygen-free radicals for metabolic derangements in the ischemic and reperfused liver is controversial. The effect on hepatic protein synthesis of a 60-minute period of ischemia followed by two hours of reperfusion was studied in four groups of rats with different hepatic contents of the oxygen free radical scavanger glutathione (GSH): group 1, fed rats; group 2, fed rats treated with diethylmaleate (DEM) one hour before use (0.69 mL/kg, i.p.); group 3, 48-hour fasted rats; and group 4, 48-hour fasted rats treated with cobalt-chloride (45 mg/kg, s.c.) ten hours before use. Protein synthesis rates were determined by measuring incorporation of U-14C-leucine into protein in incubated liver slices. Treatment of fed rats with DEM and fasting for 48 hours significantly reduced liver GSH content. The effect of fasting on liver GSH was reversed by treatment with cobalt-chloride. The protein synthesis rate was reduced to approximately 30% of initial value at the end of the ischemic period and recovered to 70% to 100% of initial value after two hours of reperfusion with no differences between the experimental groups. Thus the effect of liver ischemia and reperfusion on protein synthesis was similar in groups of rats with different hepatic GSH contents at the onset of ischemia. The data suggest that oxygen free radicals do not play a major role for the impairment of protein synthesis in the ischemic and reperfused liver.

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ALTHOUGH THE IMPORTANCE of oxygen-derived free radicals for cellular injury during reperfusion of ischemic tissue is well recognized in small intestine, heart, kidney, skin, brain, and skeletal muscle,[1–6] the role of oxygen free radicals for metabolic derangements in the ischemic and reperfused liver is controversial. For example treatment of rats with coenzyme Q 10 (CoQ 10) or alpha-tocopherol, substances that are free radical scavangers and antioxidants, prevented cellular damage and improved survival rates after liver ischemia.[7,8] In other experiments superoxide dismutase (SOD) and catalase reduced the leak of enzymes from liver cells during postischemic reperfusion, possibly reflecting improved hepatocellular integrity.[9] In contrast the same substances did not improve gluconeogenic rate or bile production during reperfusion of ischemic liver[10] and efflux of glutathione disulfide (GSSG) from postischemic liver was not increased, indicating that reactive oxygen species were not generated during reflow of the ischemic liver.[11]

Protein synthesis is an important function of the liver that is markedly reduced during and after ischemia.[12,13] In a previous study we found that restoration of protein synthesis during reperfusion of the ischemic liver was improved by the xanthine oxidase inhibitor allopurinol.[14] Because oxygen free radicals are formed during oxidation of hypoxanthine to xanthine in postischemic tissue,[15] it was suggested that the beneficial effect of allopurinol was due to reduced production of free radicals,[14] although other mechanisms may have been involved as well, such as inhibition of the irreversible breakdown of adenine nucleotides.[16] In contrast when rats were treated with SOD or catalase, either alone or in combination, before induction of liver ischemia, no beneficial effects on protein synthesis or tissue energy levels were observed in reperfused organs.[17] Thus the role of oxygen radicals for cellular injury in liver ischemia and reperfusion remains unclear.

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The present experiments were designed to study the influence of ischemia and reperfusion on hepatic protein synthesis in animals with different liver contents of an important radical scavanger, *i.e.*, glutathione (GSH).[18] GSH has been suggested to protect the liver[19-21] as well as other organs and tissues[22-25] against oxidant injury.

Materials and Methods

Four groups of male Sprague-Dawley rats weighing 330 g to 400 g were used. In group 1 fed animals had free access to food and water until use. In group 2 diethylmaleate-treated (DEM), fed rats were given a single intraperitoneal injection of DEM (0.69 mL/kg) one hour before use. This treatment was previously shown to reduce liver GSH levels.[26] In group 3 fasted rats were deprived of food 48 hours before use and were housed in wire-bottomed cages to prevent coprophagia. Group 4 cobalt-chloride-treated animals were fasted for 48 hours and were given a single subcutaneous injection of cobalt-chloride (45 mg/kg) ten hours before use. In previous studies liver GSH levels were reduced in starved rats[27] and doubled eight to ten hours after administration of cobalt-chloride.[28] Experiments were started between 8 and 9 A.M. to avoid diurnal variations of protein synthesis rates and GSH levels in liver tissue.[29]

Operative Procedures

Laparotomy was performed under light ether anesthesia and biopsy specimens were taken from the anterior edge of the left and median liver lobes for the study of protein synthesis, GSH, and glycogen (see below). Ischemia was induced by occluding the blood vessels to the left and median liver lobes with a small vascular clamp. The abdomen was closed and the animals were allowed to awaken. After one hour, new liver biopsies were taken, followed by removal of the vascular clamp. Biopsies were again obtained under light ether anesthesia one hour and two hours after reperfusion. The small bleeding from the biopsy site was controlled by gentle pressure with a sponge for one to two minutes; in a few rats it was necessary to suture the biopsy site (4-0 plain catgut).

In previous studies approximately 70% of the liver was made ischemic by occluding the blood vessels to the left and median liver lobes.[12] Because the blood vessels to the right and caudal lobes remained open, portal stasis was avoided, which is of special importance for hemodynamic stability in rats.[30] Because rats are rather unaffected by this experimental procedure, it is possible to study the isolated effects of liver ischemia.[31-33]

Protein Synthesis In Vitro

Protein synthesis rates were determined by measuring incorporation of U-14C-leucine into protein in incubated liver slices as described in detail previously.[12,14,17] The use of this *in vitro* technique to study the effects of iscehmia on hepatic protein synthesis was validated recently:[12] the precursor specific radioactivity was equal in normal and ischemic liver slices, and consequently, reduced incorporation of radioactivity into protein in ischemic liver slices reflected decreased protein synthesis; relative changes in protein synthesis after liver ischemia were similar when measured in incubated slices and *in vivo*; there was a significant positive correlation between changes in protein synthesis in incubated liver slices and changes in ATP in liver tissue during and after ischemia. Thus the current *in vitro* technique is suitable for evaluating the effects of ischemia on hepatic protein synthesis.

GSH and Glycogen Determinations

Because the purpose of these determinations was to evaluate the effect of the different treatments before ischemia was induced, *i.e.*, fasting and administration of DEM or cobalt-chloride, GSH and glycogen were determined in biopsy specimens taken before induction of ischemia. The biopsy specimens were frozen in liquid nitrogen immediately after their removal and stored at −70 C until analyzed. For measurement of GSH, biopsy specimens were homogenized in 10% trichloroacetic acid with 5 mM edetic acid and after centrifugation the amount of GSH in the supernatant was determined as described by Prins and Loos.[34] GSH levels were expressed as μmol/g wet weight. Glycogen was measured enzymatically[35,36] and glycogen levels were expressed as μmol glucose units/g wet weight.

Statistics

Results are given as mean ± SEM. Analysis of variance, followed by Tukey's test, was used for statistical comparisons between groups.

Results

GSH in liver tissue of fed rats was 7.6 ± 0.24 μmol/g ww, which was similar to previous reports.[20,28] Treatment of fed rats with DEM resulted in a fast (one hour) and pronounced reduction of hepatic GSH (Fig. 1). Also fasting reduced liver GSH, but not to the same extent as DEM treatment. The effect of fasting on liver GSH was reversed by treatment with cobalt-chloride.

Glycogen in liver tissue of fed rats was 153 ± 13 μmol/g ww and was reduced by 36% after treatment with DEM (Fig. 2). As expected, fasting for 48 h resulted in a pronounced decrease in liver glycogen. Cobalt-chloride treatment of fasted rats increased glycogen content to a small extent, but this effect was not statistically significant (Fig. 2).

Before induction of liver ischemia, the protein synthesis rate was 0.80 ± 0.07 μmol leucine/g protein x hour in

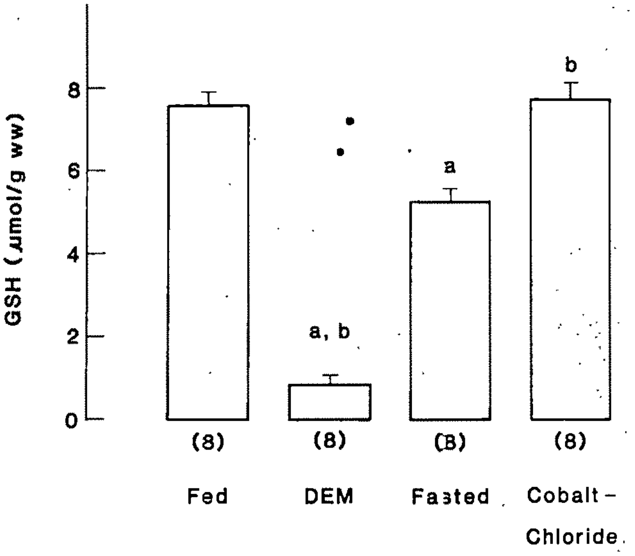

FIG. 1. GSH concentration in liver tissue of fed, DEM-treated, fasted, and cobalt-chloride-treated rats. (a) $p < 0.05$ *versus* fed rats; (b) $p < 0.05$ *versus* fasted rats.

group 1 (fed rats, n = 6). This was significantly higher ($p < 0.05$) than the initial synthesis rates in the other groups of rats: 0.38 ± 0.04 μmol leucine/g protein x hour in group 2 (DEM treated rats, n = 9); 0.47 ± 0.09 μmol leucine/g protein x hour in group 3 (fasted rats, n = 8); 0.43 ± 0.05 μmol leucine/g protein x hour in group 4 (cobalt-chloride-treated rats, n = 9). The protein synthesis rates in groups 2 to 4 are in line with previous reports in which animals were fasted for 24 hours before use.[12,14, 7,31-33]

Because each animal served as its own control, protein synthesis rates were expressed as the percentage of initial value (Fig. 3). At the end of the ischemic period, leucine incorporation was reduced to approximately 30% of initial value in all groups of rats. This reduction of protein synthesis during a 60-minute ischemic period is in good agreement with previous reports using the same experimental model.[12,14,17,31-33] During reperfusion a gradual recovery of synthetic activity was noted, and after two hours protein synthesis rates were back to initial values in fasted and cobalt-chloride-treated rats and to approximately 70% to 75% of initial values in fed and DEM treated rats. There were no significant differences in protein synthesis rates between the different groups of rats during ischemia or reperfusion.

By comparing liver GSH content (Fig. 1) with changes in protein synthesis (Fig. 3), it is obvious that the effects of ischemia and reperfusion on protein synthesis were not influenced by the amount of GSH present in the liver at the onset of ischemia. It is also obvious that basal protein synthesis rates, *i.e.*, before induction of ischemia, did not correlate with hepatic GSH content because protein synthesis rates were similar in groups 2 to 4, despite large variations in liver GSH and because protein synthesis rates were different in groups 1 and 4, despite almost identical GSH levels.

A similar comparison between liver glycogen content (Fig. 2) and protein synthesis rates suggests that there was no close correlation between these parameters. Thus liver glycogen content was higher in group 2 than in groups 3 and 4, but protein synthesis rates were similar in these groups.

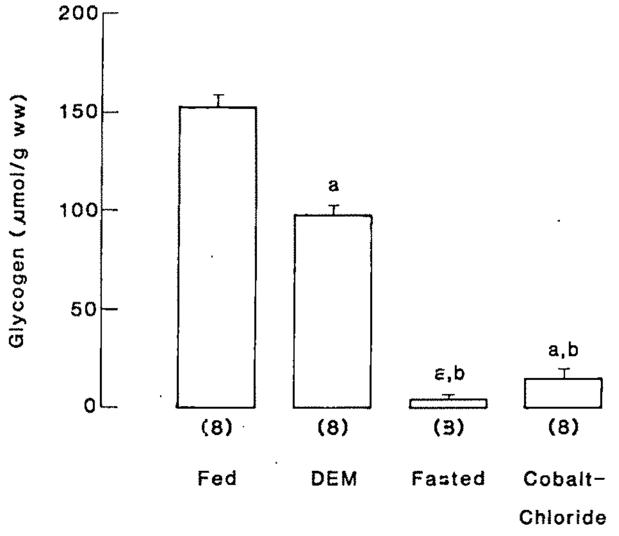

FIG. 2. Glycogen concentration in liver tissue of fed, DEM-treated, fasted, and cobalt-chloride-treated rats. (a) $p < 0.05$ *versus* fed; (b) $p < 0.05$ *versus* DEM.

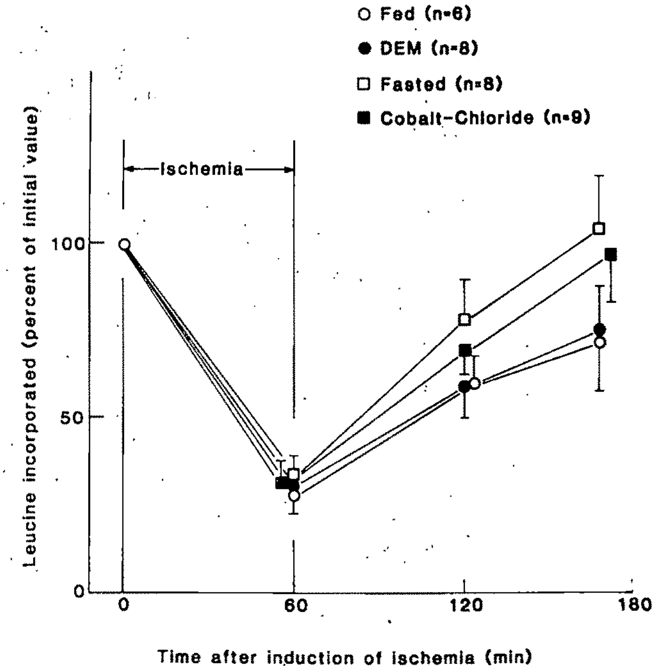

FIG. 3. Hepatic protein synthesis *in vitro* in fed, DEM-treated, fasted, and cobalt-chloride-treated rats during ischemia and reperfusion.

Discussion

The present study showed that hepatic protein synthesis was reduced during ischemia to a similar extent in groups of rats with different GSH levels in liver tissue and that recovery of biosynthetic activity during reperfusion did not correlate with hepatic GSH levels. Because GSH is an important radical scavanger,[18] the data suggest that oxygen free radicals do not play an important role for impaired protein synthesis in the ischemic or reperfused liver.

Because the purpose of the current study was to investigate protein synthesis in livers that had different GSH levels when the ischemic insult was inflicted, GSH concentrations were determined only at the onset of the experiments. It could be argued that GSH levels may have been reduced during the ischemic period, resulting in low GSH concentrations in all groups of rats at the time of reperfusion. This is not likely, however, because in previous studies liver GSH was only reduced from 7.24 to 5.82 μmol/g during 90 minutes of complete ischemia[20] and was not reduced at all when perfused livers were subjected to 120 minutes of ischemia.[11]

Glycogen levels were measured in the present study because they may be affected by fasting and by treatment with DEM or cobalt-chloride[19,38] and because large glycogen stores in fed animals have been suggested to protect the liver against ischemic insult.[37,38] Lower hepatic protein synthesis rates in starved than in fed rats are in line with previous studies in which reduced protein synthesis during fasting was associated with changes in polyribosome profiles and loss of RNA.[39] The current results suggest that protein synthesis was not influenced by liver content of glycogen in normal or in the ischemic/reperfused liver. A similar lack of protective effect of large glycogen stores was observed in a recent study in which there was no difference in the ability to preserve hepatocellular ATP levels or to maintain cellular membrane potential during ischemia between fed and fasted animals, despite ten times higher glycogen levels in the fed rats.[40] In fact a high cellular content of glycogen may even be harmful due to the risk of lactacidosis during ischemia.[41]

The possible role of oxygen free radicals for impaired hepatic protein synthesis during ischemia and reperfusion was investigated in two previous reports from our laboratory.[14,17] When rats were treated with the xanthine oxidase inhibitor allopurinol, the reduction of protein synthesis during ischemia was not affected, but protein synthesis rate during reperfusion was higher in allopurinol-treated animals than in control rats. From those observations it was concluded that oxygen free radicals, formed during reperfusion, inhibited the restitution of protein synthesis in the postischemic liver.[14] However, even if allopurinol inhibits the production of oxygen radicals during reperfusion, the substance has other effects as well,[16] and consequently the results[14] could have reflected other mechanisms than reduced production of oxygen radicals.

A subsequent study was therefore performed to further elucidate the role of oxygen radicals for hepatocellular injury in ischemia and reperfusion.[17] In that study rats were treated with catalase or SOD or a combination of the two drugs before induction of liver ischemia. There were no significant differences in protein synthesis, energy level, or tissue water between scavanger treated animals and controls, neither at the end of the ischemic period nor during a two-hour reperfusion. The results were interpreted as indicating that oxygen-derived free radicals do not play a major role for impaired protein synthesis and energy metabolism in liver ischemia or reperfusion.

One reason why administration of radical scavangers did not have a beneficial effect[17] could be that the endogenous hepatic content of radical scavangers is large enough to efficiently block the effects of oxygen radicals after ischemia. It may not be likely that administration of exogenous free radical scavangers in concentrations less than normal tissue levels can provide protection from oxygen free radicals. In the present study, therefore, the liver content of an important scavanger, *i.e.*, GSH, was manipulated by different treatments. Because results showed that the metabolic changes did not correlate with hepatic GSH levels, it is likely that oxygen radicals do not play an important role for impairment of protein synthesis in liver ischemia or reperfusion.

The two major mechanisms that have been proposed for the beneficial effect of allopurinol in ischemia are prevention of irreversible breakdown of ATP and ADP[16] and inhibition of oxygen free radical formation.[15,42] Because in our previous study it was found that allopurinol did not affect adenine nucleotide levels in the ischemic or reperfused liver, it was suggested that the beneficial effect of allopurinol on protein synthesis reflected inhibited production of oxygen free radicals.[14] However, because a previous report[17] and the present study did not support the concept of free radical-mediated impairment of protein synthesis in the ischemic or reperfused liver, it is possible that other mechanisms of allopurinol in ischemia/reperfusion must be sought. Alternatively the seemingly contradictory results between allopurinol treatment[14] and administration of SOD or catalase[17] or manipulation of liver GSH content may reflect the different modes of action between the substances. Thus it is possible that the formation of oxygen radicals must be prevented, as is the case with allopurinol, for protein synthesis to improve in the postischemic liver, while scavanging of radicals that have already been formed may be insufficient to reduce hepatocellular injury.

To the best of our knowledge, the influence of liver

GSH content on protein synthesis in the ischemic and reperfused liver has not been reported previously. However the role of GSH for other hepatocellular functions in ischemia has been reported and results were contradictory. When rats with different preischemic liver GSH content were subjected to a 90-minute period of ischemia, followed by a three-hour period of reperfusion, it was found that reduction of cellular membrane potential and early postischemic cell death, assessed by estimating intracellular calcium, were more extensive in rats with low initial GSH content and it was suggested that GSH protected the liver from reperfusion injury by reducing lipid peroxidation.[19] In other studies[20] ischemia of the rat liver resulted in a small but significant decrease in liver GSH with a further reduction during reperfusion, and it was proposed that these changes reflected consumption of GSH. Efflux of GSSG during ischemic storage of rat liver was suggested to reflect scavanging of oxygen radicals by GSH.[21]

In contrast a recent study by Jaeschke et al.[11] found no evidence that GSH is involved in the protection of the liver against ischemia/reperfusion injury. Thus when perfused livers were subjected to global ischemia for 30 or 120 minutes, liver content of GSH and GSSG were unchanged and there was no increase in biliary GSSG efflux during reperfusion, despite evidence of hepatocellular injury as reflected by lactate dehydrogenase efflux. To ensure that the protective mechanisms against reactive oxygen species were still operative in the perfused liver, a solution of the superoxide-generating compound diquat was infused. Diquat infusion resulted in a massive efflux of GSSG into bile and perfusate and an increase of tissue GSSG content as well as a decrease of hepatic GSH levels. Because ischemia and reperfusion caused hepatocellular injury without GSH consumption and GSSG generation, it was concluded that oxygen radicals are unlikely to induce ischemia/reperfusion injury in the rat liver.[11]

The present study and a previous report from our laboratory[17] suggest that scavanging of oxygen free radicals does not improve protein synthesis in the ischemic or reperfused liver. The results, however, do not preclude the possibility that other hepatocellular functions may be affected by oxygen radicals.

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Book Reviews

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The Basic Science of Vascular Surgery. Joseph M. Giordano, Hugh H. Trout III, and Ralph G. DePalma. 773 pp. Mount Kisco, New York: Futura Publishing, 1988. $89.00.

THE GROWTH AND MATURATION of vascular surgery during the past three and one half decades is evident in the establishment of Residency Review Committee-approved residency programs in general vascular surgery and certification of vascular surgeons by the American Board of Surgery. This maturation of vascular surgery has been accompanied by increased efforts to understand and update basic science data as they apply to vascular disorders and vascular surgery. This text presents a concise, yet complete, authoritative review of many of the basic science components that are important to vascular surgeons.

The 22 chapters are divided into three sections. The first nine chapters (Section I), called "Fundamental Science", include a review of the embryologic development of the vascular system and explanation of how alterations in development can lead to important aberration in anatomy and/or function. The section includes discussions of the structure, function, and physiology of the lymphatic, venous, and arterial systems. The chapters on endothelial cells, rheology, atherosclerosis, and "nonarteriosclerotic" disorders of arteries contain a wealth of information. Section II, "The Science of Ancillary Discipline," is a source of important information for the student of vascular disorders. These six chapters include discussions of grafts, lipoproteins, coagulation and hemostasis, drugs that are used in managing vascular disorders, as well as reviews of the epidemiology of arterial disorders and of basic statistics. The final seven chapters, "Selected Clinical Entities," include discussions of infections of arteries and grafts, arteriovenous fistulas, mesenteric ischemia, renal vascular disease, cerebral ischemia, and male sexual function.

This text introduces the reader to the embryology, anatomy, biochemistry, physiology, and pathophysiology of most vascular disorders. The reference list for each chapter provides ready access to in-depth reviews of the topics. This text should be readily available to all vascular surgeons and should also be in medical and surgical departmental libraries. The editors and contributors to the text are to be commended for the quality of the text and the choice of topics.

DONALD SILVER, M.D.
Columbia, Missouri

Cardiothoracic Trauma. Panagiotis N. Symbas. 404 pp. Philadelphia: W. B. Saunders, 1989. $89.00.

ELEVEN YEARS BEFORE the publication of *Cardiothoracic Trauma*, Dr. Symbas wrote *Trauma to the Heart and Great Vessels*, which has remained a landmark on the subject. With 25 years of experience in a large trauma center, Dr. Symbas is a recognized authority on the subject. Therefore much of the information in *Cardiothoracic Trauma* has been gleaned and documented from a large personal experience.

The new book is nearly twice as long and adds significantly more information. As before the literature has been covered comprehensively, updated references are complete, and historical notations are included. Also a number of new illustrations have been added to the text. Treatment algorithms, derived from the large Grady Hospital experience, are concise and easy to follow.

Additional chapters relating to pulmonary, major airway, esophageal, diaphragmatic, and chest wall injuries have been added and are complete. A new chapter covers postinjury hemopneumothorax and empyema. As in the earlier book, coverage of blunt and penetrating cardiac trauma is excellent. Cardiac tamponade, contusion, rupture, and traumatic septal defects, as well as pericardial, coronary, and valve injuries are well discussed. Methods for diagnosing cardiothoracic injuries have been updated in these chapters.

There are very few deficiencies or omissions in the new book. Although detailed descriptions of surgical technique were minimized purposely, important features of each operation are included. For repairing descending aortic injuries, partial cardiopulmonary bypass was mentioned; however discussion of heparinless vortex pumps (Biomedicus) was omitted. Because intraoperative epicardial and transesophageal echocardiography have been helpful recently for localizing retained missiles, septal defects, and valve injuries, some chapters may have been strengthened by reviewing these diagnostic modalities.

In summary the impact of *Cardiothoracic Trauma* resides not in detailed descriptions of surgical techniques, but rather on early recognition, rapid resuscitation, and appropriate therapy for each injury. Moreover Dr. Symbas discusses each injury from a pathophysiologic standpoint, thus strengthening the text. The book represents an excellent update and should be helpful to senior surgeons and residents alike.

W. RANDOLPH CHITWOOD, JR., M.D.
Greenville, North Carolina

Lower Extremity Amputation. Wesley S. Moore and James M. Malone. 368 pp. Philadelphia: W. B. Saunders, 1989. $65.00.

DESPITE SIGNIFICANT ADVANCES in vascular surgical techniques that permit many ischemic and badly traumatized limbs to be salvaged, amputations continue to be required. The editors of this text, Wesley Moore and James Malone, have had a long and deep interest in lower extremity amputation surgery and in all phases of the care and rehabilitation of the amputee. Rather than considering amputation an admission of defeat, they have adopted a positive attitude that permeates the pages of this book. Contributors, chosen for their expertise, cover in logical sequence preservation of the ischemic limb, management of the diabetic foot, selection of amputation site, anesthesia, operative techniques, application of immediate fit prostheses, surgical complications, prosthetic design, and physical and psychosocial therapy. In addition there are two interesting chapters concerning the pathophysiology of amputation, energy expenditure, and the biomechanics of ambulation.

Inevitably, as in any multiauthored text, there is some redundancy, which is not necessarily a drawback because it allows many chapters to stand alone. An introductory chapter summarizing the history of amputation, the magnitude of the problem, the psychosocial and fiscal impact of amputation, and the potential for rehabilitation would have been useful. Although most of this information can be found in the book, it requires some searching. The seven chapters on selection of amputation site, while providing a balanced approach, contain contradictory material; and the uninitiated reader may come away with no distinct plan for applying the noninvasive methods that are discussed. A particularly challenging area, amputations of the foot, is covered in insufficient detail. For example Lisfranc's and Chopart's disarticulations are mentioned, but no description is given of the operative techniques. Free tissue transfer is not considered. Photographs, some of which are hard to interpret and are of marginal quality, have been used to illustrate the crucial steps in procedures such as Syme's amputation. Line drawings, like those used in most atlases, would have been preferable.

There are a number of particularly good chapters, including the contribution on pain management, which outlines a pragmatic approach to this most difficult and devastating problem. The reference list is extensive and the index is good. While this book has some deficits, these are more than counterbalanced by its overall value to the general and vascular surgeon, who will find that it constitutes a comprehensive source of information on all aspects of amputation surgery and rehabilitation.

DAVID S. SUMNER, M.D.
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Cancer of the Bile Ducts and Pancreas. Paul E. Preece, Alfred Cuschieri and R. David Rosin. 352 pp. Philadelphia: W. B. Saunders Co., 1989. $79.00.

THE BOOK ENTITLED *Cancer of the Bile Ducts and Pancreas* is a collective effort by renowned surgeons and physicians in the field, which is edited by three surgeons from the British Isles. The 328-page book features an extensive index, with a thorough and up-to-date reference list included with each chapter. The initial chapter provides an excellent review of the epidemiology, etiology, and pathology of bile duct tumors. The chapters that divide the cholangiocarcinomas into proximal, distal, and ampullary categories are extremely well written, and the chapters on interventional radiology, radiotherapy, and endoscopic stenting provide essential information. However the four chapters concerning morphology, markers, and estrogen receptors in pancreatic cancer could have been condensed into one chapter. The second chapter, an overview of malignant obstruction, could easily have been omitted because the material is covered elsewhere, and Chapter Four's review of recent data from the Bristol area of England does not warrant a separate chapter. The remainder of the book concentrates primarily on endocrine and exocrine tumors of the pancreas and their treatment and is a comprehensive review of the subject. The chapters concerning therapy for adenocarcinoma of the pancreas related to surgery, chemotherapy, and radiation therapy are particularly useful in this respect.

This text represents a relatively complete work on many of the tumors that cause malignant jaundice. The text may be somewhat tedious for day-to-day use, but it certainly represents an excellent resource on the subject. This is facilitated by its thorough indexing and the long list of references for each chapter. I recommend it for those interested in graduate level diagnosis, treatment, and research in the field of bile duct and pancreatic cancers.

THEODORE N. PAPPAS, M.D.
Durham, North Carolina

Endovascular Surgery. Wesley S. Moore and Samuel S. Ahn. 572 pp. Philadelphia: W. B. Saunders Co., 1989. $90.00.

THE EDITORS OF this book have accurately identified the tremendous interest in the developing endovascular treatment techniques and have produced a small, well-written volume providing basic information on these techniques addressed primarily to the practicing physician.

Unfortunately a reader seeking a thoughtful assessment of the current role of the evolving techniques of endovascular therapeutic manipulation in the treatment of patients with peripheral vascular disease will not find it in this volume as, with rare exception, both the editors and chapter authors are clearly enthusiastic proponents of the new techniques. Anecdotes abound and critical assessments of therapeutic efficacy are indeed rare, if not totally absent.

The volume consists of 540 pages, divided into four primary sections of about equal length. Sections include vascular endoscopy, balloon angioplasty, mechanical atherectomy, and laser and thermal angioplasty. This relatively small volume presents the reader with 51 chapters authored by 77 authors, a virtual cast of thousands in keeping with modern book preparation techniques. The strengths of the book are considerable. The publisher has done a highly professional job: the photographs are clear, the text is concise with minimal typographical errors, the quality of paper is excellent, and the book is a pleasure to scan as well as to read carefully. The volume is a handy compilation of available data on the various techniques. Almost every topic in the broad field of endovascular interventional techniques is covered in this volume. A number of references accompany each chapter, allowing the interested reader to pursue the topics in more depth. Several of the chapters are outstanding. The history of angioscopy by Dr. Victor Bernhard is one of these, as is the insightful and delightfully irreverent chapter by Dr. Robert Ginsburg on laser angioplasty as an adjunct to balloon dilatation.

Unfortunately weaknesses also abound in this volume. There is an agonizing amount of repetition in these chapters, which suggests a lack of a firm editorial hand in chapter assembly. Similarly a number of outrageous statements can be found in these chapters. In one section, the virtues of iliofemoral venous thrombectomy are extolled, while in another we learn that thromboendarterectomy is the arterial reparative method of choice for aortoiliac disease with ten-year patency rates of 95%.[1]

In nearly every chapter in which clinical results are described, the accepted standards of clinical reporting, including precise endpoints and life-table data presentation, are ignored. The authors seem content to describe merely "patency" figures, whatever that means. The absence of rigorous use of standard conventions for reporting patency renders the clinical portions of this volume completely anecdotal.

This book appears remarkably well timed to meet a widely perceived need. Because almost every community hospital in America seems to be adding rapidly angioscopy, atherectomy, and laser angioplasty to its patient care facilities, this book should be well received as a handy reference source by individuals entering these new fields. I would have welcomed a more critical and thoughtful assessment of the role of the emerging modalities in patient care. I believe it is equally likely that each of these techniques will be relegated ultimately to the dust bin as to the forefront of vascular surgery. Only time will tell. At $90.00, the book seems to be reasonably priced and generally well done. It is recommended for those seeking a convenient up-to-date reference on the emerging techniques of endovascular diagnosis and treatment.

JOHN M. PORTER, M.D.
Portland, Oregon

Rob & Smith's Operative Surgery: Pediatric Surgery (4th Edition). Hugh Dudley, David Carter, and R.C.G. Russell, General Editors; Lewis Spitz and H. Homewood Nixon, Consultant Editors. 703 pp. Stoneham, MA: Butterworths, 1988. $250.00.

THIS SECOND EDITION of the *Pediatric Surgery* volume brings together sections by 65 authors from all over the world. Edited by the very experienced and world-renowned Lewis Spitz and H. H. Nixon, it provides a very complete compendium of pediatric surgical topics ranging from congenital head and neck lesions through the usual thoracic, abdominal wall, and gastrointestinal abnormalities to common lesions of the neuroaxis and extremities. Urologic anomalies are treated extensively by a most knowledgeable group of pediatric surgeons and pediatric urologists, and in keeping with its strong United Kingdom foundation, myelomeningocele, hydrocephalus and other spinal dysraphisms are presented in effective detail.

Introductory chapters dealing with the transport of the newborn for surgery, preoperative and postoperative management, and pediatric anesthesia have been appropriately added and are generally effectively presented. I would quarrel with the advice for a nasogastric tube for transport in a newborn who is a known obligate nose breather, however. Marc Rowe's preoperative and postoperative management chapter is excellent, in keeping with this surgeon's great knowledge of these subjects. With such otherwise excellent general chapters on these topics, it is unfortunate that the authors of many of the subsequent chapters on specific entities include their own recommendations regarding transport, fluid management, anesthesia, and other aspects of preoperative, intraoperative, and postoperative care that conflict with the general chapters and are frequently less effective in their advice.

As part of a massive 17-volume treatice on operative surgery, this *Pediatric Surgery* volume is meant to provide adequate information and illustrations to enable surgeons, particularly in remote parts of the world where easy referral to a pediatric surgery center may not be available, to deal with the many pediatric surgical anomalies. This volume generally provides good-to-excellent discussions of the entities, but frequently fails to provide detailed enough illustrations to accomplish the goal. In reading each chapter with the question of whether I could perform the operation from the material presented, I found that frequently, even for procedures with which I was very familiar, I became confused and for some with which I have had little experience, I could not fathom the approach. Much of this is due to inadequate labeling of otherwise well-done illustrations. For a considerable part of my venture through the book, I thought that an editorial decision to avoid labels such as arrows, letters, and so on, had been made, but then one comes to chapters such as that on cleft lip and palate that are effectively illustrated and one wonders why others are deficient. An example of a chapter with excellent illustrations of rather complex surgical interventions is Hardy Hendren's "Urinary Diversion and Undiversion," and Jay Grosfeld's "Neuroblastoma" contains excellent, well-labeled illustrations.

Because every surgeon believes that his way of doing things is superior, it is always difficult to review a text of operative procedures without taking exception to many approaches. However there are specific areas of deficiencies in some chapters that merit correction in future revisions. These include the failure to mention the importance of exercise for torticollis and absence of a discussion of the craniofacial abnormalities resulting from failure to resolve the torticollis lesions; the conflict between preauricular sinus described as a branchial remnant in the chapter on branchial clefts and subsequently as the more widely accepted "sinus of the helix" in the separate chapter on preauricular sinus; the absence of any mention of primary repair (*versus* interposition) for wide-gap esophageal atresia; the advice to use alpha- and beta-blocking agents in all neurogenic tumors—neuroblastomas, the overwhelmingly most common neurogenic tumor in childhood, almost never secrete clinically significant levels of catecholamines; the statement at the conclusion of the inguinal hernia chapter that "a transient rise in temperature in the first postoperative 24 hours is almost invariable"; the recommendation in the splenectomy chapter that polyvalent pneumococcal vaccine be given after (rather than before) splenectomy!

In discussing gastroschisis, there is no mention of the tremendous fluid losses and potential hypovolemic shock commonly seen with this entity, and the 10 to 14 days outlined for closure of the prosthetic sac is too long and usually results in severe sepsis. I thought it unfortunate that Mr. Nixon's very succinct discussion of Meckel's diverticulectomy failed to include the interesting embryology of the omphalomesenteric duct.

The section on portal hypertension has well-illustrated discussions of the shunts presented but fails to mention the widely preferred Warren distal splenorenal shunt.

The problem of individual authors presenting their own narrow views of a subject can best be overcome by having a knowledgeable, experienced, and well-respected surgeon comment on each presentation with the express purpose of pointing out appropriate alternatives.

Despite these criticisms, this is a most worthwhile effort and contains a vast array of important knowledge. It should prove to be a good source for understanding the basics of most of the common pediatric surgical procedures.

HOWARD C. FILSTON, M.D.
Durham, North Carolina

Principles of Organ Transplantation. M. Wayne Flye. 687 pp. Philadelphia: W. B. Saunders, 1989. $125.00.

IT HAS ONLY BEEN 35 years since the first successful living related kidney transplant between identical twins was performed at the Peter Bent Brigham Hospital. With kidney transplantation as the model, subsequent achievements in the field of clinical transplantation have been unsurpassed in medicine. Science is frequently accused of confining its discoveries too long to the laboratory before they are permitted clinical applications. Dr.

Flye and his collaborators demonstrate in *Principles of Organ Transplantation* that for clinical transplantation this has not been the case. The remarkable progress has been possible only because of the close collaboration between basic immunology, clinical transplantation, and individuals who have been able to bridge the two disciplines. In this book and in choosing his collaborations, Dr. Flye has effectively demonstrated this bridging effect. Those basic areas that are responsible for this rapidly advancing discipline are expertly dealt with in the book. These can be divided broadly into three categories: I. transplantation immunobiology, including immunogenetics, graft modification, principles of allograft rejection, immune monitoring, and immunosuppression; II. organ preservation and handling, including brain death, selection criteria, and anesthetic considerations in the transplant patient; and, III. surgical techniques in which the spectrum of topics ranges from the time-tested operative approach to renal and cardiac transplantation to the still-evolving techniques in pancreas transplantation. All these areas are handled either individually in separate chapters or are woven into those chapters dealing with the individual organs. More time is spent on renal transplantation because this has been the model on which all other extrarenal organs have based their progress. However every organ that is now being transplanted clinically or extensively studied in the laboratory has its own chapter. Each collaborator is a recognized authority in his area. The book is best suited to the individual with a background knowledge of the science of clinical transplantation who is seeking an overview of current knowledge and the discoveries that have allowed this remarkable progress. The book is both practical and scientific in its treatment of the field and is recommended for all students of transplantation.

BRACK G. HATTLER, JR., M.D., PH.D.
Pittsburgh, Pennsylvania

Letters to the Editor

May 11, 1989

Dear Editor:

I was very interested to see the article on the physiologic approaches to the control of obesity by Powers and Pappas in the March 1989 issue of *Annals of Surgery.* However I was very distressed to see the description of the gastric bypass given in the article from a paper that was 20 years old. The procedure as done now, is quite different from that which is described in the paper, and a review article on the subject should have reflected the more current procedure. At the present time, the stomach is no longer divided but is stapled instead. Furthermore the gastrojejunal anastomosis is much more narrow than that described by Drs. Powers and Pappas, usually in the range of 1 cm or less.

In the article there is an accurate description of the vertical banded gastroplasty, but no mention of the complications. While complications are listed in the paragraph above on gastric bypass, this is not comparably mentioned in association with gastroplasty. This is quite inaccurate and complications for the latter operation are also relatively common, and are actually somewhat similar to those of the gastric bypass. I believe that omitting any mention of complications may imply that there are none. I think that this is an oversight. Furthermore, in terms of results in the several randomized studies between these two procedures, it appears that the gastric bypass is more effective in terms of weight loss. I think that in reviewing the subject as the authors did, it might have been appropriate to report these findings with accuracy.

At any rate I do feel that the inaccurate description of current gastric bypass procedure is a major failing in this article. If this article had been published in a basic science or medical journal rather than a surgical one, and by physiologists or internists rather than by surgeons, one could possibly excuse this with the rationalization that the authors were unfamiliar with the literature and, considering the audience of the journal, it may not matter. However, when this article is published as the lead article of the most prestigious surgical journal, it is very distressing. It also makes me wonder whether this article was really reviewed before publication, and if so, how careful were the reviewers. It has been my experience that when I have submitted a paper to *Annals of Surgery*, it is reviewed in great detail and depth. What went wrong in this case?

At the least I think these authors should publish an addendum in a future issue of the journal that describes the current procedure of gastric bypass and lists the complications of the vertical banded gastroplasty procedure.

NORMAN B. ACKERMAN, M.D., PH.D.
New York, New York

May 23, 1989

Dear Editor:

We are pleased to have this opportunity to respond to several comments and criticisms that Dr. Norman Ackerman has concerning the article entitled "Physioloic Approaches to the Control of Obesity" (Ann Surg 1989; 209:255–260). Apparently he misunderstood the major thrust of the manuscript in that he considers it to be a comprehensive review of surgical techniques for morbid obesity. The purpose of the paper was actually to "discuss the physiologic mechanisms that affect satiety in animals and man." For that reason, the clinical aspects of surgery for obesity were relegated to one or two paragraphs in this manuscript. We acknowledge that devoting this small amount of the manuscript to surgery for morbid obesity did not allow a comprehensive review of techniques and complications. With those comments in mind, we would like to respond to Dr. Ackerman's specific criticisms.

Dr. Ackerman is concerned that we quoted a 1969 paper on gastric bypass. It is the common practice to quote original manuscripts concerning techniques that were relatively new in their day. That is not to imply that these concepts or procedures have not been modified with time. The manuscript of Drs. Mason and Ito was quoted because it was innovative in 1969 and still represents an important contribution in the gastric bypass literature. The use of the term "divide" implies anatomically divided, which can be done by physically dividing the stomach or stapling across it. We apologize if that was not made clear in the manuscript. The actual size of the anastomosis draining the small pouch varies among authors, but Dr. Ackerman is correct that the general trend has been toward smaller and smaller anastomoses. Not including the operative complications of vertical banded gastroplasty was not an oversight in this manuscript. The purpose was not to compare gastric bypass to vertical banded gastroplasty but was, instead, to present an overview suggesting that neither operation successfully treats all cases of obesity. The mention of complications in the section on gastric bypass was simply to highlight the fact that these are relatively complex operations on high-risk patients and are fraught with complications. It is true that the complication rate is similar for vertical banded gastroplasty, but as we stated earlier, our purpose was not to suggest that one operation was better than the other.

Undoubtedly Dr. Ackerman feels that our article should serve as a reference for the complete description of the nuances of gastric bypass *versus* vertical banded gastroplasty. If this is the case, I am certain he will continue to be disappointed. If the readers of the *Annals of Surgery* are interested in a careful description of the current procedure for gastric bypass and a detailed list of complications of vertical banded gastroplasty, they should not refer to our article, but should instead consult the many other studies in the literature whose intent is to review all clinical surgical aspects of intervention for morbid obesity.

THEODORE N. PAPPAS, M.D.
MARY A. POWERS, M.D.
Durham, North Carolina

April 5, 1989

Dear Editor:

In a 24-hour ambulatory study, Eriksen et al.[1] failed to detect significant differences in the duodenal pH of healthy controls and patients with active duodenal ulcers and conclude that duodenal ulcer formation is not primarily due to exposure of the bulb mucosa to acid. We do not believe that this study can support the authors' conclusions.

Although a pH sampling rate of once every 20 seconds may be acceptable for the assessment of intragastric pH (in which rapid changes in pH are uncommon), it is grossly inadequate for duodenal recordings,[2,3] and would result in an excessive loss of information. Furthermore, when attempting to assess bulb pH, it is vital that artefactual recordings due to proximal displacement of duodenal pH electrodes into the antrum can be recognized and discarded from the analysis. Electrode displacement is known to occur after food intake, changes in body position, and alterations in gastrointestinal motility,[2] and we do not believe that a fluoroscopic check at the end of the study is adequate proof that the recording electrodes remained in a satisfactory position for 24 hours. Indeed the inherent inaccuracy of studies relying on intermittent localization of duodenal pH electrodes is underlined by our observation[4] that even when maintaining electrodes within the bulb by monitoring transmucosal potential difference across the pylorus, (thus allowing displacement to be recognized and, when possible, instantly corrected), between 0% and 25% (median 5%) of each study was discarded due to incorrect placement of the pH probes.

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DAVID KERRIGAN, F.R.C.S., F.R.C.S.(Edin.)
NIGEL BIRD, B.SC.
ALAN JOHNSON, M.A., M.CHIR., F.R.C.S.
Sheffield, England

July 17, 1989

Dear Editor:

We appreciate the interest of the authors in our recent publication and note that they disagree with the conclusions reached on two issues: sampling rate and displacement of the duodenal electrode. Both criticisms, although legitimate in principle, were addressed in the published article but require further comment.

While few would dispute that there must be an optimal sampling rate to record pathophysiologic events, which indeed may be different in the various organs (esophagus, stomach, duodenum), there is no evidence in the reported literature on prolonged pH duodenal monitoring (scanty as it is) to suggest that the sample rate we used was "grossly inadequate," and the two references quoted by Kerrigen et al.[1,2] have no specific data on this issue. There is indeed a problem with having a portable ambulatory system with the necessary capacity to permit frequent sampling (60/minute) over a 24-hour period, especially when two electrodes are used. When this technical problem is overcome, perhaps with data compression systems, studies to evaluate the ideal sampling rate to assess prolonged duodenal acid exposure and pathophysiologic events would be preferable to armchair predictions based on short-term studies performed mainly with gastric and esophageal pH. The importance of rapid acid peaks in the pathophysiology of duodenal ulcer disease is unknown and their influence on the acid exposure over a 24-hour period is doubtful.

Migration of the duodenal pH electrode is a well-recognized problem with pH monitoring of the *base of the duodenal bulb.* In addition the sharp pH gradient (pH 3.3 at the base, 4.2 in mid portion and 5.1 at the apex) is well documented.[3] With these considerations in mind, we placed the duodenal probe at the apex of the bulb (junction of first with second parts of the duodenum). This is clearly outlined in the text and in the illustration. Furthermore the use of the weighted mercury bag in the upper jejunum ensured fixation and its efficacy in this respect has been documented in several previous reports.[4–6]

There is need for more clinical studies on prolonged dual gastroduodenal pH patients with duodenal ulcer disease and one expects that with technical developments in ambulatory monitoring, more detailed studies will be possible. Until then the role of acid as a primary pathogenetic factor in duodenal ulcer disease remains questionable.

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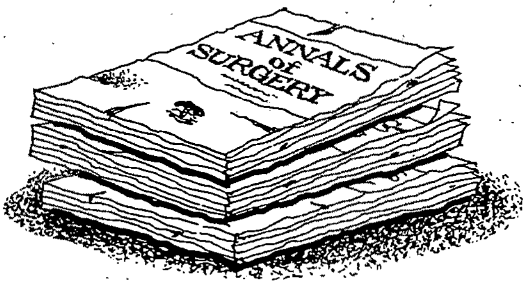

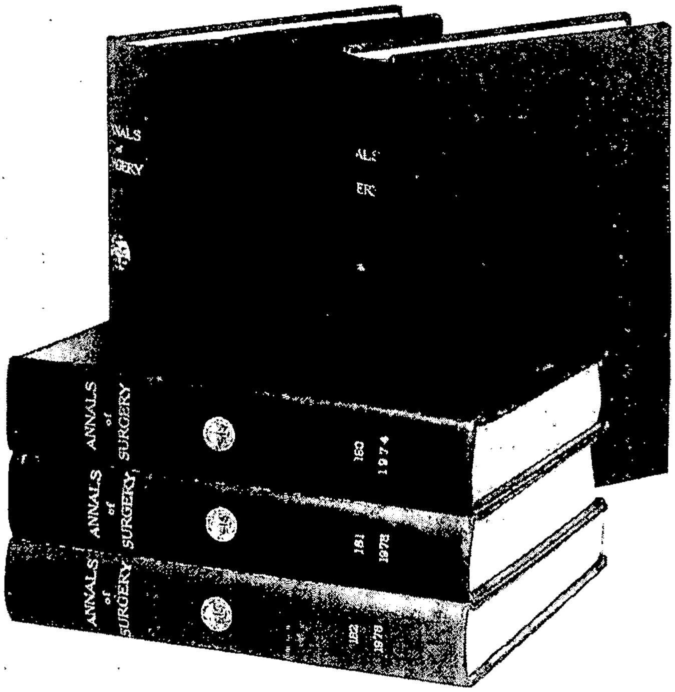

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What's New
In General Surgery

Management of Traumatic Retroperitoneal Hematoma

DAVID V. FELICIANO, M.D.

The management of retroperitoneal hematomas remains confusing to many surgeons because the available literature frequently groups patients with blunt and penetrating etiologies together. Because the underlying injuries and their treatment may differ considerably, the nonoperative or operative approach to the common hematomas is based on mechanism of injury coupled with hemodynamic status of the patient and extent of associated injuries. After blunt trauma, selected retroperitoneal hematomas in the lateral perirenal and pelvic areas do not require operation and should not be opened if discovered at operation. Midline, lateral paraduodenal, lateral pericolonic not associated with pelvic, and portal hematomas are opened after proximal vascular control has been obtained, if appropriate. Retrohepatic hematomas without obvious active hemorrhage are not opened. After penetrating trauma, most retroperitoneal hematomas are still opened. Exceptions include isolated lateral perirenal hematomas that have been carefully staged by CT and some lateral pericolonic hematomas. As with blunt trauma, retrohepatic hematomas without obvious active hemorrhage are not opened.

WHILE RETROPERITONEAL HEMATOMAS are not rare in hospitals caring for traumatized patients, controversies about appropriate management continue. One reason for this is the policy of many authors to draw conclusions from series combining patients with blunt and penetrating retroperitoneal injuries. This is inappropriate because the sources of hemorrhage and natural history of the hematoma differ considerably depending on the etiology. For example the morbidity and mortality from a retroperitoneal hematoma around a kidney contused by blunt trauma are considerably different from those caused by a gunshot wound to the renovascular structures. Another reason for controversy and confusion has been the advances in radiologic imaging that now allow for a more precise evaluation of injuries to retroperitoneal structures without the need for operation. The management of retroperitoneal hematomas has continued to evolve based on information gained from these newer diagnostic modalities. Finally retroperitoneal hematomas from blunt trauma usually demand multidisciplinary care.[1] Yet communication between the involved specialties, especially in the available literature, appears to be lacking. For example recent surgical papers concerned with the control of retroperitoneal hemorrhage from blunt pelvic fractures continue to suggest that bilateral ligation of the internal iliac arteries remains a viable therapeutic alternative. This will, of course, preclude precise pelvic arteriography and therapeutic embolization of

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deep arterial bleeders by an interventional radiologist in the postoperative period if the bilateral ligation fails.

This review will focus on current diagnostic approaches to injuries in retroperitoneal structures that may cause hematomas and will differentiate between the therapy indicated for blunt *versus* penetrating etiologies of retroperitoneal hematomas.

Definition

The retroperitoneal space lies posterior to the sac of the peritoneal cavity and contains completely or envelops anteriorly a number of visceral and vascular structures in the gastrointestinal, genitourinary, vascular, musculoskeletal, and nervous systems.[2] Injury to gastrointestinal structures such as the distal esophagus, the second, third, and fourth portions of the duodenum, the pancreas, the posterior parts of the ascending and descending colon and the flexures of the colon, and the rectum may produce retroperitoneal hematomas easy to ignore or miss at operation. Injury to genitourinary structures such as the kidneys, adrenal glands, ureters, and bladder may be obvious on preoperative radiologic screening even before a surrounding retroperitoneal hematoma is discovered at operation. Injury to vascular structures such as the abdominal aorta and inferior vena cava and their branches or retroperitoneal branches of the portal venous system may present with either a contained retroperitoneal hematoma or exsanguinating hemorrhage.[3] Finally injuries to musculoskeletal structures such as the psoas major, quadratus lumborum, and iliacus muscles, the diaphragm, and the vertebral bodies from penetrating wounds or the pelvic bones from blunt trauma are common causes of retroperitoneal hematomas.

Incidence

The incidence of retroperitoneal hematomas based on etiology in three combined series since 1980 has been blunt—80%, 70%, 67% *versus* penetrating—20%, 30%, 33%.[4-6] In one oft-quoted series of 171 patients admitted with blunt trauma, 44% had a retroperitoneal hematoma documented at laparotomy (97%) or autopsy (3%).[7] Grieco and Perry classified their 80 patients with blunt trauma and a retroperitoneal hematoma into a perirenal group (45%), pelvic group (28.8%), and an "other" group (26.2%).[4] Selivanov et al.,[5] using the classification described at the San Francisco General Hospital, divided 57 patients with retroperitoneal hematomas from blunt trauma into a pelvic group (zone III, 70.2%), flank or lateral group (zone II, 22.8%), and a upper to mid-central group (zone I, 7%).

In patients with penetrating wounds, the incidence of retroperitoneal hematomas is unclear. In 1966 Steichen et al.[8] noted that 5.9% of patients undergoing laparotomy for penetrating wounds of the abdomen had "hemorrhage in the retroperitoneal space." At the time of that report, less selective criteria for performing laparotomies after penetrating abdominal trauma were in place. Also recent reports from urban trauma centers caring for large numbers of patients with gunshot wounds of the abdomen have documented a 25% incidence of abdominal vascular injuries at the time of laparotomy.[9,10] Presumably many or most of these patients with abdominal vascular injuries present with retroperitoneal hematomas rather than exsanguinating hemorrhage at the time of laparotomy.

Mechanism of Injury

The mechanism of injury in patients suffering blunt trauma is best described as a moving or stationary victim striking or being struck by a moving or stationary object or surface. Any of these mechanisms will cause sudden contact with compression, deceleration with deformation, or both.[11] The magnitude of injuries that occur is related to the kinetic energy of the victim at the time of impact. Pelvic fractures result from contact with the inside of the car or femur. A pelvic retroperitoneal hematoma is caused by the loss of blood from sites of fractures, disruption of multiple veins in the posterior pelvis, and disruption of deep pelvic arteries, which are often distal branches from the internal iliac vessels. Perirenal hematomas result from either contact with the inside of the car or adjacent deformed or fractured ribs or from deceleration. Direct contact may lead to contusions, lacerations, polar avulsions, or ruptures, while deceleration may avulse the renal vein or its branches or disrupt the intima of the renal artery with secondary thrombosis. Blunt rupture of the second or third portion of the duodenum presenting as a periduodenal retroperitoneal hematoma is thought to be secondary to a direct blow with compression or shearing against the spine or a closed loop blowout from deceleration. In patients with midline retroperitoneal hematomas from blunt trauma, deceleration with avulsion of small branches from the aorta, inferior vena cava, superior mesenteric artery, or portal vein beneath the pancreas is the most common cause. Less often a midline transection of the pancreas over the spine caused by contact with the lower rim of the steering wheel is present.

The mechanisms of injury in patients suffering penetrating trauma include (1) contact of body parts with a knife; (2) contact of body parts with a missile, its fragments, or secondary missiles such as teeth or spicules of bone; or (3) cavitation as caused by high-velocity missiles. The magnitude of injuries that result depends on the structure and content of the organ that is hit by a knife or missile and on the kinetic energy of the missile at the time of contact or the size of its cavitation field. In civilian life the narrow blade used in most stabbings or the lowvelocity missile fired from a handgun causes a small entrance wound into the retroperitoneum. The previously mentioned tamponading effect of the retroperitoneum is lifesaving in many patients with retroperitoneal injuries from penetrating wounds. This is most noticeable in patients with penetrating wounds to the suprarenal or infrarenal aorta in which the pressure exerted by the retroperitoneal hematoma slows the rate of hemorrhage and allows for salvage rates of 35% and 45%, respectively, in modern trauma centers.[12]

Classification

Numerous classification systems of retroperitoneal hematomas now exist and make comparison of management techniques from different centers difficult. Some of the available classification systems are summarized in Table 1.[3,6,13,14]

Diagnosis

Clinical

The symptoms and signs of a retroperitoneal hematoma are most commonly a reflection of the organs injured in the retroperitoneum rather than of the hematoma itself. Pain in the anterior abdomen, flank, back, or pelvic area may be present, depending on the etiology. On examination signs of hypovolemic shock are usually present in patients with significant pelvic fractures or penetrating wounds to the aorta, inferior vena cava, or major branches. Because a Grey-Turner's sign is usually not present during the first day after injury, it is not helpful in the early diagnosis of a retroperitoneal hematoma. Laboratory findings such as anemia and hematuria from an associated renal contusion or injury to the bladder or male urethra is common when a significant pelvic fracture has occurred. Hyperamylasemia, especially when it progressively increases during the first 24 to 48 hours after injury, strongly suggests the presence of injury to either the pancreas or duodenum.[15]

Radiologic Approach—Blunt Trauma

The radiologic approach to the patient with blunt trauma and a suspected retroperitoneal hematoma is based on the patient's condition and the surgeon's suspicion about which retroperitoneal organs may have been injured. A plain film of the abdomen in which there is obliteration of the psoas muscle shadow or displacement of gas-filled organs by a mass suggests the presence of a retroperitoneal hematoma.[2] This is more likely to be true if associated fractures to the pelvis, lumbar vertebrae, or lower ribs are present. The presence of air in the right upper abdomen outlining the lateral aspect of the duodenum (Fig. 1), coupled with obliteration of the upper psoas muscle border on the right, scoliosis of the lumbar spine to the left, or air in front of the first lumbar vertebra on a lateral x-ray of the abdomen all suggest retroperitoneal rupture of the duodenum under the hematoma.

In the stable patient with a history of a direct upper midline blow but no x-ray findings suggestive of duodenal rupture, it is worthwhile to insert a nasogastric tube and inject air into it. A repeat abdominal x-ray is then performed to see if retroperitoneal air is now present. More commonly water-soluble radiologic dye has been injected into the tube while the patient is lying on his or her right side. Any extravasation of dye on another abdominal x-ray documents the presence of a duodenal perforation. In recent years computerized tomography (CT) performed with a combination of ingested and intravenous contrast (enhanced CT) has been used to document the diagnosis instead of the studies mentioned above.

TABLE 1. *Classification Systems of Retroperitoneal Hematomas*

Shaftan, 1980*	Kudsk and Sheldon, 1982†	Henao and Aldrete, 1985‡	Feliciano et al., 1988§
Abdominal	Central-medial (zone 1)	Central	Midline supramesocolic (includes lesser sac)
Midline		Vascular Peripancreatoduodenal	Midline inframesocolic
Flank Perirenal Pericolonic	Flank (zone 2)	Flank	Lateral perirenal, paraduodenal, and pericolonic
Pelvic Anterior Posterior Unilateral Bilateral	Pelvic (zone 3)	Pelvic	Pelvic
		Combined	Portal and retrohepatic

* Shaftan GW. Retroperitoneal trauma. Contemporary Surgery 1980; 16:25–35.

† Kudsk KA, Sheldon GF. Retroperitoneal hematoma. *In* Blaisdell FW, Trunkey DD, eds. Abdominal trauma. New York: Thieme-Stratton, 1982: 279–93.

‡ Henao F, Aldrete JS. Retroperitoneal hematomas of traumatic origin. Surg Gynecol Obstet 1985; 161:106–16.

§ Modified from Feliciano DV, Burch JM, Graham JM. Abdominal vascular injury. *In* Mattox, KL, Moore EE, Feliciano DV, eds. Trauma. East Norwalk: Appleton & Lange, 1988. pp. 519–36.

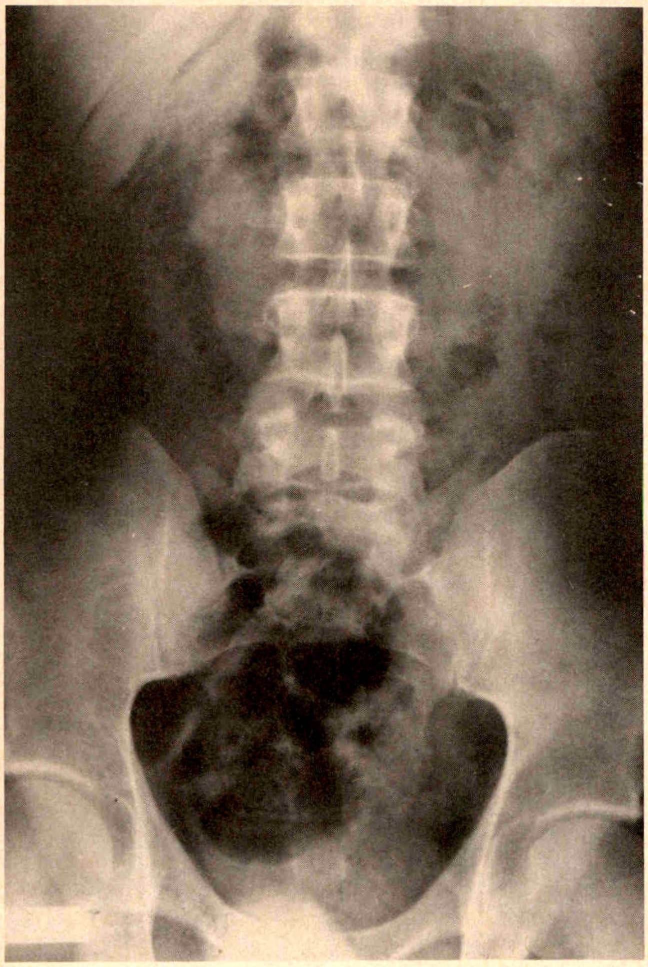

FIG. 1. Retroperitoneal air in right upper quadrant outlining C loop of the ruptured duodenum.

As previously mentioned, persistent or progressive hyperamylasemia after blunt upper-abdominal trauma in the absence of other indications for laparotomy mandates further radiologic studies. CT is an excellent technique to evaluate the pancreas, and Jeffrey et al.[16] have been able to distinguish between mild traumatic pancreatitis involving diffuse swelling of the gland and transection of the organ (Fig. 2). AN ERCP is useful when CT is not available or is equivocal, and there is a continuing concern about the presence of a pancreatic ductal injury in the mildly symptomatic patient.[17–19]

Hematuria in the stable patient who has sustained a direct blow to the flank has most commonly been evaluated by intravenous pyelography (IVP) in the past. A recent study has suggested that this examination is worthwhile only in patients with more than 30 red blood cells per high-power field, but it continues to be used liberally in most centers.[20] An IVP confirms the presence of two functioning kidneys and may document an injury in either a kidney or ureter. CT is preferred by many urologists as the next diagnostic step in a patient with significant hematuria and an abnormal IVP because the examination is highly sensitive and accurate[21] (Fig. 3). The presence of hematuria and nonvisualization of one kidney on an IVP has usually prompted a selective renal arteriogram to rule out the presence of thrombosis of a renal artery secondary to deceleration; however CT has been used with increasing frequency in recent years when this diagnosis is suspected. If a soft-tissue image of the kidney is present but there is no enhancement or only modest cortical enhancement from adrenal arteries when intravenous contrast is given, then renal arterial flow is absent. It has also

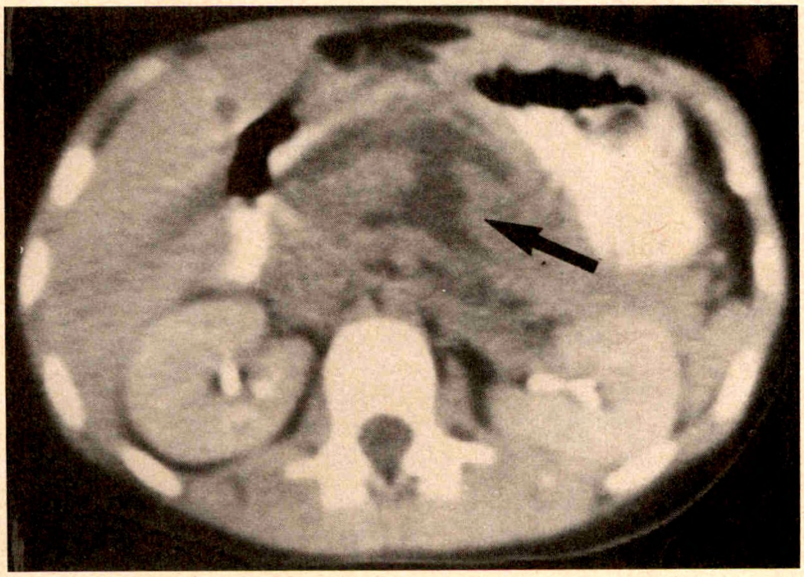

FIG. 2. Transection of the body of the pancreas over the spine on CT (From Feliciano DV. *In* Schwartz SI, Ellis H, eds. Maingot's Abdominal Operations, 9th ed. East Norwalk, CT: Appleton & Lange, 1989: publication pending. Reprinted with permission.)

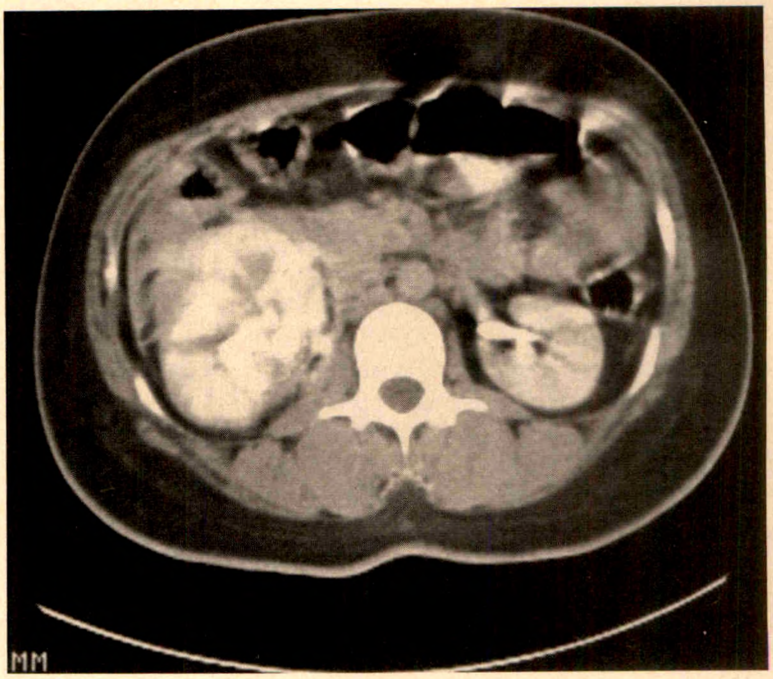

FIG. 3. Right renal laceration on CT performed after abnormal IVP.

been suggested that the absence of hematuria in a patient with significant abdominal trauma strongly suggests the need for an IVP to determine if renal artery flow is intact.[22]

Should a pelvic fracture be present in a patient with hematuria, a retrograde cystogram is indicated to rule out a rupture of the bladder in an anterior retroperitoneal hematoma. This is preceded by a retrograde urethrogram in patients who cannot void, have a floating prostate gland, and blood at the urethral meatus. In the past, an intravenous pyelogram would then be used to complete the evaluation of the genitourinary system. CT is now used in place of an IVP in such a patient in many centers because both the kidneys and the pelvic fractures can be rapidly evaluated.[23]

In an occasional (2% to 3%) patient with a pelvic fracture, persistent need for transfusion, and no evidence of intra-abdominal visceral injury on DPL and CT, pelvic arteriography is performed. Deep pelvic bleeding from distal branches of the internal iliac artery such as the superior gluteal, internal pudendal, or obturator arteries can be diagnosed and treated (to be discussed).

Radiologic Approach—Penetrating Trauma

A plain film in a patient with a penetrating wound from a missile will localize the site of the missile and give some indication of which retroperitoneal visceral or vascular structure might be injured.

In the stable patient with hematuria after a penetrating wound near the kidney, an IVP is performed for the same purposes as in the patient with blunt trauma and hematuria. The stable patient with hematuria and a transpelvic stab or gunshot wound will also undergo a preoperative retrograde cystogram to rule out perforation of the bladder in some centers.

One area of major concern in asymptomatic patients with stab wounds to the back is that an occult penetrating injury to the posterior surface of the duodenum, pancreas, ascending colon, descending colon, kidneys, or a vascular structure may have resulted. Hemorrhage can be tamponaded by the retroperitoneum with posterior stab wounds to any of these organs, and symptoms of organ penetration may be minimal for days or even weeks in certain individuals. One radiologic technique that has been used is administration of dye through nasogastric tube, enema, and IV before a CT scan to visualize all the retroperitoneal structures that might be injured by the stab wound. This so-called contrast-enhanced CT enema has proved to be accurate and has lowered the incidence of nontherapeutic laparotomies in centers in which it has been used.[24]

Diagnostic Peritoneal Lavage—Blunt Trauma

Diagnostic peritoneal lavage (DPL) as a complementary study to CT continues to be used to evaluate patients with blunt abdominal trauma and possible retroperitoneal hematomas.[25] Most commonly it has been used to rule out rapidly the presence of intraperitoneal injuries in patients with pelvic fractures. The incidence of such associated injuries varies depending on the magnitude and type of the fracture. In Murr and Moore's series, the incidence was 16% overall and 40% in patients with Malgaigne fractures.[26] This latter figure is similar to the 36% reported for Malgaigne fractures in Peltier's review.[27] In a more recent review, Cryer et al.[28] noted a 45% incidence in patients with unstable, open-book, lateral compression, or vertical shear pelvic fractures.

The major problem with the standard infraumbilical technique has been the large number of false-positive examinations in patients with pelvic fractures and associated retroperitoneal hematomas.[29–32] In such patients, a careful open approach through the supraumbilical area or at the infraumbilical ring is recommended to avoid passing the lavage catheter through the anterior extension of a retroperitoneal hematoma or into the posterior retroperitoneal hematoma itself.[1,33] A tear in the posterior peritoneum will, of course, lead to a false-positive DPL in most patients.

In stable patients with pelvic fractures, CT would be the diagnostic test of choice rather than DPL in many modern trauma centers.[23] In unstable patients (not exsanguinating), many of whom will have a pneumatic antishock garment (PSAG) in place, the trauma center staffs at Denver General Hospital, the Mayo Clinic, and the University of Louisville will perform a supraumbilical DPL to rapidly determine the presence of intraperitoneal bleeding.[1,34–36] It is of interest that the DPL is performed in the operating room in Louisville.[34] A patient whose preliminary diagnostic peritoneal tap or lavage return is grossly bloody will then undergo emergent laparotomy to control presumed intraperitoneal hemorrhage. Pelvic fixation is also performed under this anesthetic, depending on the type of fracture, the hemodynamic status of the patient, and the progression of the pelvic retroperitoneal hematoma during the laparotomy. Continued progression of the hematoma or need for postlaparotomy transfusion would mandate pelvic arteriography with selective arterial embolization.[1,34–36]

A patient whose DPL is positive based on red blood cell count alone can undergo further studies or therapeutic maneuvers such as CT of the head, immediate pelvic fixation, or visceral arteriography. The Hermann Hospital in Houston has used visceral arteriography in reasonably stable patients with this DPL result to verify whether active visceral hemorrhage, which would mandate laparotomy, is occurring.[37] This is performed in association with standard pelvic arteriography and therapeutic embolization, as needed.

Retroperitoneal Hematoma After Blunt Trauma

Nonoperative Management of Selected Patients

In patients with signs of significant intra-abdominal blood loss, overt peritonitis, or both after sustaining blunt trauma, laparotomy is recommended. Other stable asymptomatic or mildly symptomatic patients will undergo general evaluation by the diagnostic studies previously discussed.[16,20,21,24,31,32] Many patients in this latter group may have documented intra-abdominal visceral injuries to the kidney, spleen, or liver, bony pelvic injuries, and associated or presumed retroperitoneal hematomas; however, laparotomy is not recommended.

Patients with Perirenal Retroperitoneal Hematomas. The first group of patients in whom nonoperative management is usually chosen includes those with hematuria, limited renal injuries, and a perirenal retroperitoneal hematoma.[38–41] Approximately 95% of patients with blunt renal injuries fall in this group.[42] If radiologic evaluation with an IVP, nephrotomogram, ultrasound, CT, or renal arteriogram reveals only a renal contusion, there is uniform opinion that nonoperative management is indicated because all of these kidneys are normal on late follow-up.[42,43] The management of patients with more severe injuries such as superficial (cortical) lacerations, deep (medullary) lacerations, urinary extravasation, polar avulsion, or blunt rupture associated with a perirenal retroperitoneal hematoma remains controversial. While superficial lacerations are usually managed nonoperatively, persistent or late complications such as continuing hematuria or reduced parenchymal activity have been reported.[42,43] Cass et al.[43] noted that the delayed renal surgery rate has been 13% to 68% in the available literature during the past 20 years and was 53% in his own series when nonoperative management of the more severe degrees of renal injury was chosen. As a general rule, the patient with a deep (medullary) laceration, extensive urinary extravasation, polar avulsion with more than 20% of the kidney nonviable, rupture of the kidney, renovascular injury, and a perirenal retroperitoneal hematoma on preoperative radiologic screening should undergo renal exploration.[21,41–43]

Patients with Pelvic Retroperitoneal Hematomas. As previously noted pelvic retroperitoneal hematomas associated with pelvic fractures are caused by bleeding from a variety of sites, none of which is usually amenable to direct surgical control.[44–46] Hemorrhage from sites of fractures may be slowed or stopped by the application of a PASG[1,47–50] or early external skeletal fixation,[51–53] while venous hemorrhage from venous plexuses or smaller veins should be tamponaded by the intact retroperitoneum.[1,48,54] The rare patient with a deep pelvic arterial bleeder can be managed by therapeutic embolization.[35–37,54–60] Therefore stable patients or unstable (not exsanguinating) patients without evidence of intraperitoneal injuries on physical examination, DPL, arteriography, or CT can be managed nonoperatively when retroperitoneal hematomas from pelvic fractures are present.[1,35–37,54]

Exceptions to nonoperative management for pelvic retroperitoneal hematomas include (1) patients with exsanguination secondary to the pelvic fractures or associated intra-abdominal injuries[35,54] (Fig. 4); (2) patients with rupture of the hematoma through open perineal wounds (open pelvic fractures)[61–63]; and (3) patients with known or suspected major vascular injuries within the retroperitoneal hematoma.[64–67] Rothenberger et al.[66] have suggested that hypotensive pedestrians with open pelvic fractures and a double break in the pelvic ring are at highest risk for major vascular injuries and should undergo early operation.

Operative Management

Laparotomy is performed after blunt trauma in symptomatic patients and in asymptomatic or mildly symptomatic patients with DPL or radiologic evidence of major visceral or vascular injuries. Certain retroperitoneal hematomas discovered at laparotomy for blunt trauma should always be opened (Table 2). Other hematomas, such as the selected perirenal and pelvic hematomas previously discussed, should not be opened when the appearance at operation conforms to the preoperative clinical and radiologic evaluation (Fig. 5). Should the hematoma in either of these groups rapidly expand, become pulsatile, or rupture, it is usually opened; however not all surgeons would agree with this approach.

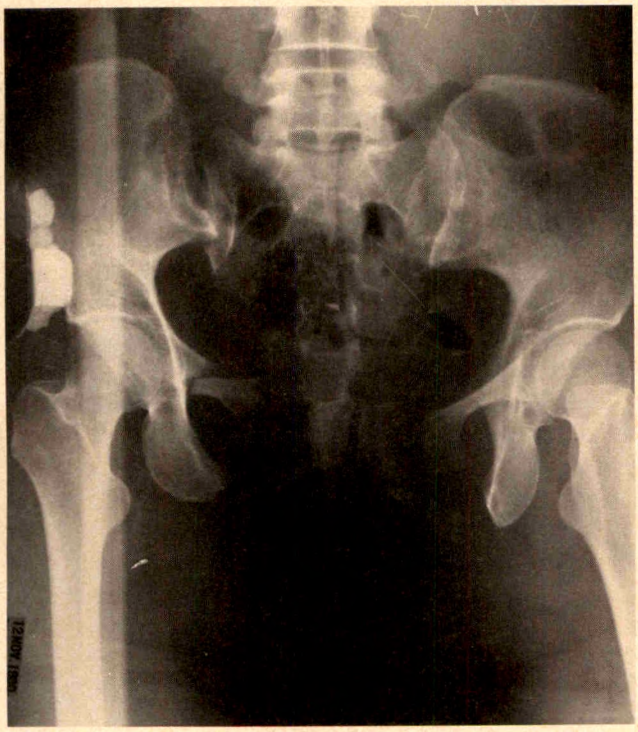

FIG. 4. Patient with multiple pelvic fractures after being run over by a bus required immediate operation because of exsanguinating hemorrhage.

TABLE 2. *Operative Management of Retroperitoneal Hematomas After Blunt Abdominal Trauma**

Location	Approach at Operation
Midline supramesocolic	Open hematoma†
Midline inframesocolic	Open hematoma†
Lateral	
Perirenal	Do not open if preoperative IVP, ultrasound, or CT reveals reasonably intact kidney
Paraduodenal (bile staining, crepitus, etc.)	Open hematoma to rule out duodenal perforation
Pericolonic	Open hematoma to rule out colonic injury, if not associated with pelvic hematoma
Pelvic	Do not open if pelvic fracture present, rate of expansion is slow, arterial pulsations intact in groins, and urethrogram and cystogram are normal
Portal and retrohepatic	
Portal	Open hematoma to rule out injury to common bile duct or portal vein†
Retrohepatic	Controversial. Do not open in stable patient if no obvious active hemorrhage after hepatic injury treated

* Modified from Feliciano DV. Abdominal trauma. In: Schwartz SI, Ellis H, eds. Maingot's Abdominal Operations. East Norwalk: Appleton & Lange, 1989 (publication pending).

† After obtaining proximal and, if possible, distal vascular control.

Midline Supramesocolic Retroperitoneal Hematoma. This hematoma should be opened after obtaining proximal and, if possible, distal vascular control because a major vascular injury may be present.[68–75] While a major blunt injury to the suprarenal aorta (SRA) is extraordinarily rare,[73,74] avulsion of the superior mesenteric artery (SMA) from its origin has been reported from several trauma centers.[68–72] More commonly avulsion of small posterior branches of the SRA is present. Proximal control of the SRA and its branches is obtained with a medial mobilization of all left-sided intra-abdominal viscera, including the left colon, pancreas, spleen, left kidney, and fundus of the stomach (Fig. 6). The aorta is most easily exposed after this mobilization by making a left radial phrenotomy incision and dissecting the distal thoracic aorta or abdominal aorta in the hiatus superior to the celiac nerve plexus and surrounding lymphatics.[3] An alternative approach is to open the lesser omentum, pull the esophagus to the left, and come down directly on the aorta just inferior to its hiatus.[76] An aortic clamp is then applied to the supraceliac aorta before the supramesocolic retroperitoneal hematoma is opened. Dissection proceeds distally until the SRA, origin of the SMA, and origin of the left renal artery are inspected. If avulsion of the SMA is found, back-bleeding from the avulsed end can be con-

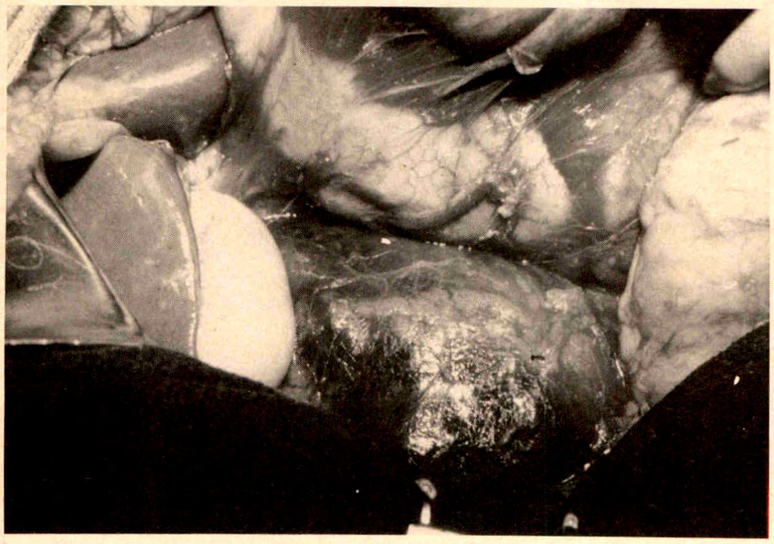

FIG. 5. Right perirenal hematoma was not opened at laparotomy after preoperative radiologic screening revealed that kidney was reasonably intact.

trolled by application of a vascular clamp or insertion of a Fogarty balloon catheter into the orifice. Options for repair of blunt avulsion of the SMA include reimplantation into the aorta, ligation with dependence on distal collateral flow, or bypass grafting from a more distal site on the abdominal aorta to the distal end of the SMA.[68]

A small supramesocolic hematoma or a retroperitoneal hematoma at the base of the transverse mesocolon may be the sole external manifestation of a blunt thrombosis of the renal artery secondary to an intimal tear. The decision to attempt revascularization depends primarily on the length of time elapsed since occlusion was thought to occur. In one review there was an 80% chance of restoring some renal function after 12 hours of occlusion, but this decreased to 57% if the occlusion had been present for 18 hours.[77] Some surgeons have chosen to revascularize the ischemic kidney only when other intra-abdominal injuries mandate laparotomy and less than 12 hours have elapsed since injury.[78]

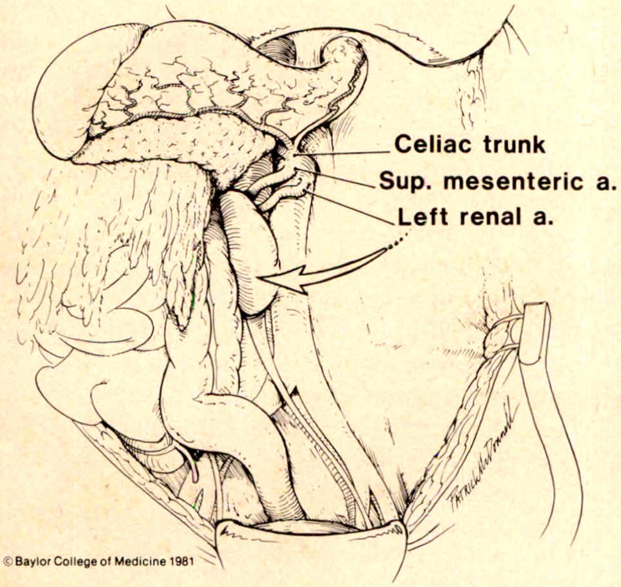

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FIG. 6. Medial rotation of all left-sided intra-abdominal viscera allows visualization of the entire abdominal aorta, including the hiatal or diaphragmatic, suprarenal or visceral, and infrarenal portions.

Blunt venous injuries that may cause a supramesocolic hematoma include avulsion of the left renal vein or of small peripancreatic branches of the portal vein. Avulsion of the left renal vein has most commonly occurred after a severe direct blow to the epigastrium. As proximal control would not ordinarily be obtained because of the rarity of this condition, control of hemorrhage may be difficult after the retroperitoneal hematoma is opened. Lateral venorrhaphy is performed if a partial avulsion is present, although ligation of the vein near the midline (with or without nephrectomy) may be required. Avulsed peripancreatic veins are ligated, and the pancreas is drained depending on the magnitude of the capsular injury.

A midline supramesocolic retroperitoneal hematoma in the lesser sac may contain a transected pancreas rather than a vascular injury. This injury has been missed on numerous occasions because of reluctance to mobilize the pancreas, open the hematoma under the thin mesothelial capsule of the pancreas, evacuate the clot, and visualize the transection[79] (Figs. 7 and 8). When present blunt transection is often to the right of the midline and much closer to the head of the pancreas than is commonly illustrated in textbooks. Surgical options, once a pancreatic transection has been confirmed, include distal pancreatectomy with or without splenectomy or a Roux-en-Y distal pancreatojejunostomy.[79]

Midline Inframesocolic Retroperitoneal Hematoma. Avulsion of posterior lumbar branches of the infrarenal abdominal aorta or inferior vena cava accounts for most hematomas in this location. Active hemorrhage is rare,

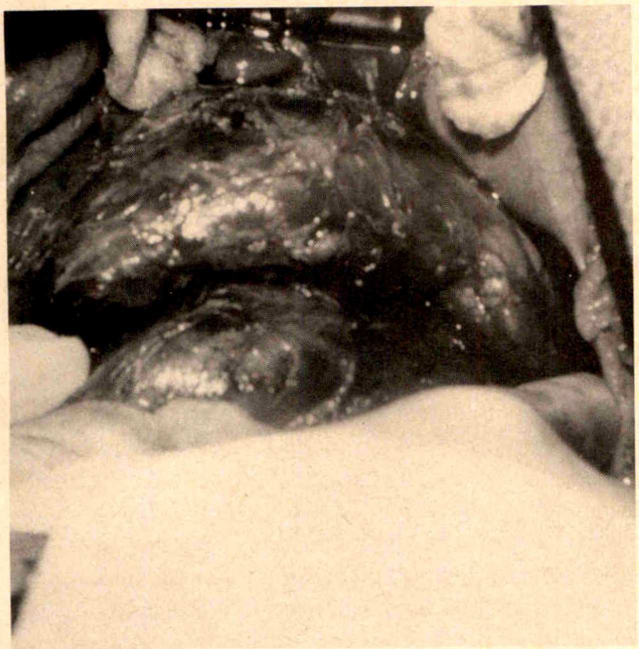

FIG. 7. Peripancreatic hematoma after blunt trauma (From Feliciano DV. *In* Schwartz SI, Ellis H, eds. Maingot's Abdominal Operations, ninth edition. East Norwalk, CT: Appleton & Lange, 1989: publication pending. Reprinted with permission.)

but exploration is mandatory to verify that a lumbar artery is not bleeding. The infrarenal abdominal aorta is exposed inferior to the base of the mesocolon to obtain proximal control. The inferior vena cava may be exposed in this fashion also; however medial mobilization of all right-sided intra-abdominal viscera except the right kidney along with a Kocher maneuver will allow visualization of the entire infrahepatic inferior vena cava (Fig. 9).

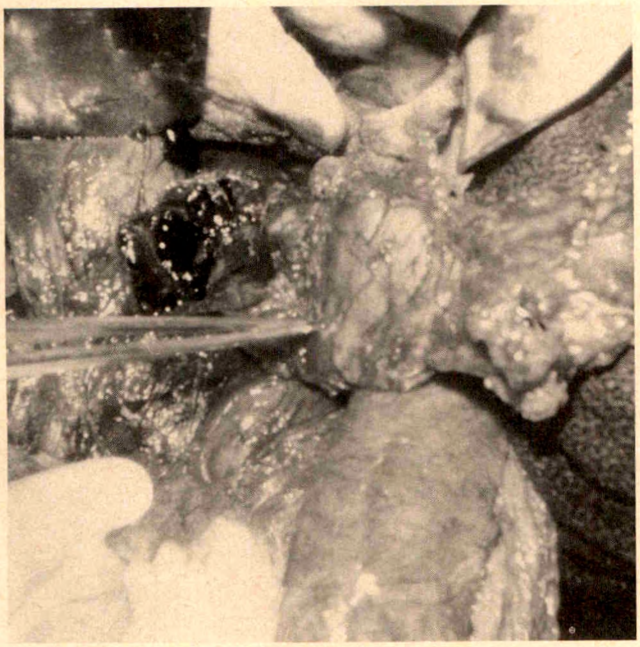

FIG. 8. Transection of the pancreas discovered when the hematoma seen in Figure 7 was opened. (From Feliciano DV. *In* Schwartz SI, Ellis H, eds. Maingot's Abdominal Operations, 9th ed. East Norwalk, CT: Appleton & Lange, 1989: publication pending. Reprinted with permission.)

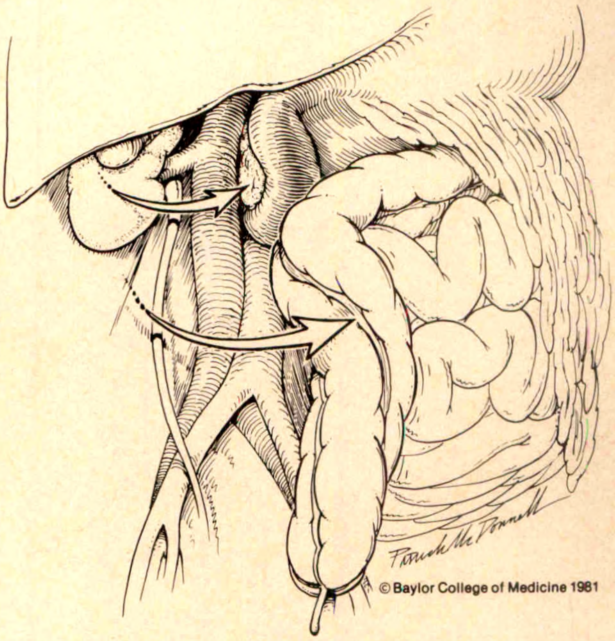

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FIG. 9. Medial rotation of all right-sided intra-abdominal viscera except the right kidney allows visualization of the entire infrahepatic inferior vena cava.

Lateral Perirenal Retroperitoneal Hematoma. As previously noted exploration is favored by many urologists if preoperative radiologic staging indicates that a more severe degree of renal injury is present underneath the hematoma or if rapid expansion, a pulsatile nature, or free rupture of the hematoma is present.[41–43,80,81] A perirenal retroperitoneal hematoma is opened only after proximal renovascular control has been obtained at the midline for the left-sided vessels or at the midline and after a Kocher maneuver for the right-sided vessels[81] (Fig. 10).

On rare occasions a retroperitoneal hematoma in a location more superior to that of a standard perirenal hematoma may contain an avulsed right adrenal vein. This hematoma should also be opened if this injury is suspected, and the inferior vena cava should be repaired with 5-0 or 6-0 polypropylene sutures.

Lateral Paraduodenal Retroperitoneal Hematoma. Because of concern about the presence of a perforation or blowout of the second or third portion of the duodenum under a lateral paraduodenal retroperitoneal hematoma, this hematoma should be opened. In many patients palpable crepitus or visible bile staining under the hematoma will make the diagnosis obvious before the hematoma is opened. A small perforation is repaired in two layers in

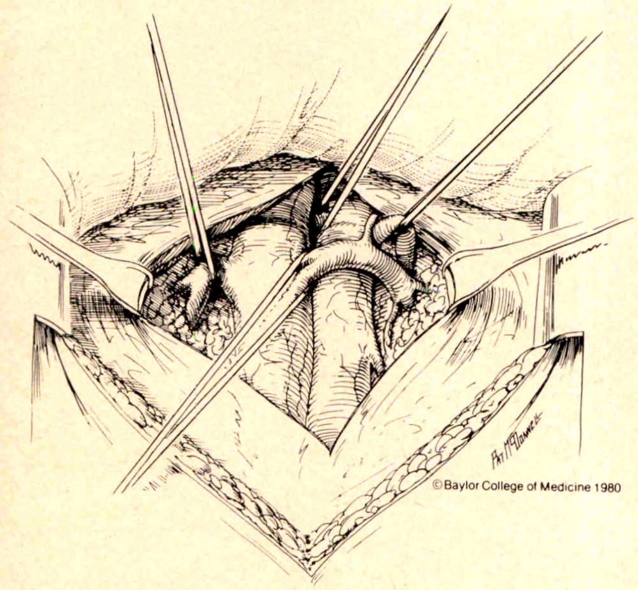

FIG. 10. Renovacular control is obtained before opening a perirenal hematoma.

a transverse direction, while more extensive blowouts or near transections are treated by debridement and an end-to-end anastomosis, Roux-en-Y (side) duodenojejunostomy, or conversion to a Roux-en-Y (proximal end) duodenojejunostomy with stapling or overviewing of the distal end of the duodenum.[82,83] Protective proximal diversion or decompression of the duodenal repair may be obtained by technical adjuncts such as duodenal diverticulization, pyloric exclusion with gastrojejunostomy, or insertion of triple tubes.[84–87]

Lateral Pericolonic Retroperitoneal Hematoma. Pelvic retroperitoneal hematomas frequently extend and involve the posterior aspect of the ascending and descending colons and gutters outside these structures. A pericolonic hematoma that is clearly an extension of a pelvic retroperitoneal hematoma is ordinarily not opened if the colon itself shows no signs of a direct injury. A completely separate pericolonic hematoma is more suggestive of direct blunt trauma to the colon, an admittedly rare injury, and should be opened to verify integrity of the colonic wall.[88]

Pelvic Retroperitoneal Hematoma. This blunt hematoma discovered at laparotomy (*i.e.*, was not an indication for laparotomy) is not opened in the presence of (1) pelvic fracture; (2) slow rate of expansion during laparotomy; (3) intact arterial pulsations in the groin; and (4) normal preoperative urethrogram and cystogram. Therefore exploration is indicated when one of the following is present: (1) ruptured hematoma (either into peritoneal cavity or perineal wound) or pulsatile (suggesting the presence of an arterial injury); (2) rapidly expanding hematoma with no other source of exsanguination (major vascular injury likely; no time for transfer to arteriography suite); (3) lack of arterial pulsation in a groin (arterial injury present); or (4) intraperitoneal rupture of the bladder or rupture or transection of the male urethra.

In the presence of a ruptured, pulsatile, or rapidly expanding hematoma, proximal control of the infrarenal abdominal aorta and inferior vena cava should be obtained. The small bowel is pulled to the right, the sigmoid colon to the left, and the midline retroperitoneum is opened proximal to the sacral promontory. Vascular looping of these structures is not necessary in young trauma patients because the placement of an aortic cross-clamp or caval spongesticks is relatively easy once a modest amount of dissection has been performed. Distal vascular control of the external iliac vessels is obtained just proximal to the inguinal ligament after these vessels have come out of the pelvis. If careful dissection of major named arteries and veins does not reveal an injury, the surgeon has a dilemma. The time-honored technique of bilateral hypogastric artery ligation[89] is usually unsuccessful in controlling exsanguinating bony and venous hemorrhage directly associated with the pelvic fractures and is not selective enough to control the uncommon deep pelvic arterial bleeders.[1,35,36,46,54,90–92]

There are several options for the surgeon at this point. If the continuing hemorrhage appears to be venous or bony in origin, the pelvis is packed tightly with nonopaque gauze and the midline incision rapidly is closed. A towel clip closure of the skin only, which has been used in selected distended, shocky, or packed patients after abdominal trauma in recent years, is not appropriate in this situation because the interpretation of subsequent pelvic arteriograms would be compromised.[93] If the packing slows hemorrhage and the patient's blood pressure stabilizes, immediate external fixation of the pelvic fractures is indicated. When rapid continuing hemorrhage from the depths of the pelvis appears to be arterial in origin and cannot be controlled by packing, intraoperative arteriography through the hypogastric arteries is indicated. A bleeding point from a distal branch of one hypogastric artery demonstrated on the operative arteriogram can be controlled by proximal ligation and the passage of a Fogarty balloon catheter[94,95] into the offending vessel or by intraoperative embolization performed by the surgeon.[96] Finally a patient with only modest control of hemorrhage or expansion of the hematoma during packing should undergo immediate pelvic arteriography with therapeutic embolization.

The patient who has continuing pelvic hemorrhage from a ruptured retroperitoneal hematoma despite application of a PASG, attempts at operative control, insertion of pelvic packs, application of an external fixator, or attempted therapeutic embolization is theoretically a candidate for hemipelvectomy as a lifesaving maneuver.[1,54,96] In truth, this procedure has essentially been reserved for patients whose original injury mandates that it be done.[97,98]

Thrombosis of the common or external iliac artery is a rare manifestation of crushing pelvic injuries.[67,99] Failure to recognize or treat this problem will result in a lower extremity amputation rate of at least 50%.[100] If profound hypovolemic shock, disruption of arterial collaterals by extensive soft-tissue injuries, and use of the PASG are also present, essentially all patients will require a major amputation of the ipsilateral lower extremity.[67] Options for repair include interposition grafting in the pelvic hematoma, bypass grafting (iliofemoral) around the point of occlusion, or insertion of an extra-anatomic femerofemoral bypass using an 8-mm externally supported PTFE prosthesis.[3]

While extraperitoneal rupture of a bladder containing sterile urine is usually managed nonoperatively, intraperitoneal rupture mandates laparotomy. The anterior wall of the bladder is exposed through any extension of the pelvic retroperitoneal hematoma and is opened to expose the site of rupture.[42] A double layer closure of the intraperitoneal site of rupture with absorbable sutures is performed. This is coupled with seven to ten days of drainage through a cystostomy tube placed in the anterior wall of the bladder and will usually lead to a satisfactory repair.

Posterior rupture of the male urethra associated with a pelvic fracture is most commonly treated in a preliminary fashion by operative insertion of a suprapubic cystostomy tube that remains in place for 3 months.[101] At that time dilatation of a stricture or formal excision of the strictured area with reanastomosis can be performed with excellent results.

Portal and Retrohepatic Retroperitoneal Hematomas. A hematoma in the area of the porta hepatis should be opened because injury to either the common bile duct, common hepatic duct, or portal vein may be present. Blunt injuries to the extrahepatic biliary ductal system are thought to be due to sudden upward motion of the liver with secondary avulsion at the fixed points of the duct, specifically just above the head of the pancreas and at the bifurcation of the hepatic duct.[102–104] If this injury is not diagnosed, the chronic biliary leak will lead to jaundice, biliary ascites, inanition, and, eventually, death. A partial avulsion of a biliary duct may be repaired in a primary fashion, with the role of stents still controversial.[103,105] Complete transections from avulsing trauma are best repaired with a bilioenteric anastomosis using a Roux-Y limb.[104,105]

Blunt injuries to the portal vein are rare and most commonly represent avulsions of branches from the wall. The presence of a dark (nonbilious) hematoma in the porta should prompt the application of a proximal vascular clamp (Pringle maneuver) to all structures in the hepatoduodenal ligament before the hematoma is opened.[106] Repair of the injured portal vein is preferably accomplished by lateral venorrhaphy in a transverse direction using 5-0 or 6-0 polypropylene sutures; however even such simple repairs may be thrombosed on postoperative angiograms or ultrasound examinations.[107] More complex repairs such as end-to-end anastomoses, portacaval shunting, and venous shunts have been used with success on occasion, as has ligation.[108–110] If ligation is necessary, splanchnic hypervolemia will lead to a several-day period of peripheral hypovolemia. Stone and associates[110] have emphasized the need for vigorous fluid resuscitation in the early postoperative period in these patients.

A retrohepatic retroperitoneal hematoma should not be disturbed if no active hemorrhage occurs once an overlying hepatic injury is treated.[93] If moderate bleeding from the area of the hematoma occurs with manipulation of the overlying lobe and multiple intra-abdominal injuries are present, the insertion of perihepatic packs for a 24-to-48-hour period may be more efficacious than originally thought.[111] Exsanguinating hemorrhage from the area of the hematoma that increases with manipulation of the overlying hepatic lobe strongly suggests blunt injury to the hepatic veins or retrohepatic vena cava. Partial vascular control may be attained by insertion of a transcardiac atriocaval shunt using either a #36 chest tube or #8 endotracheal tube and application of a Pringle maneuver before attempting venous repair.[112,113]

Retroperitoneal Hematoma After Penetrating Trauma

Nonoperative Management of Selected Patients

In patients with signs of significant intra-abdominal blood loss, overt peritonitis, significant evisceration, hematemesis, or proctorrhagia after sustaining penetrating trauma, laparotomy is recommended. Other stable asymptomatic or mildly symptomatic patients who have suffered stab wounds and even gunshot wounds with peritoneal penetration now undergo a variety of evaluations to avoid an unnecessary laparotomy. For example patients with anterior abdominal or flank stab wounds have been safely screened with either DPL or a period of observation in many trauma centers.[114,115] Similarly observation alone has been very successful in avoiding unnecessary laparotomy for patients with stab wounds and gunshot wounds of the back.[116] CT has been used to avoid laparotomy in patients with stab wounds or gunshot wounds to the flank or back, hematuria, and a known renal injury.[81] Finally the previously described contrast-enhanced CT enema has been used to screen patients with stab wounds or gunshot wounds of the pelvis or back.[24] All of these techniques are extremely accurate and, hence, successful in avoiding unnecessary laparotomies in patients who do not have gastrointestinal perforation, vascular perforation, continuing hemorrhage from solid organs, or have only limited renal injuries. Many of these patients have flank or retroperitoneal hematomas that will never be explored.

Operative Management

The aphorism that all retroperitoneal hematomas associated with penetrating wounds must be opened is no longer completely true. Certain retroperitoneal hematomas discovered at laparotomy for penetrating trauma should still always be opened, but there is debate about some others, much as in patients with retroperitoneal hematomas from blunt trauma (Table 3). A comprehensive description of all the available repairs for vascular injuries in retroperitoneal hematomas associated with penetrating wounds is beyond the scope of this report, and the reader is referred to available publications.[3,106,117]

Midline Supramesocolic Retroperitoneal Hematoma. This hematoma should be opened after obtaining proximal and, if possible, distal vascular control. The left-sided medial mobilization maneuver and left phrenotomy at the aortic hiatus allow clamping of the supraceliac aorta under direct vision before opening the hematoma (Fig. 6). Dissection then proceeds distally until the surgeon determines if the injury is to the SRA, celiac axis, proximal SMA, or proximal renal artery.[3,117] Exposure for distal vascular control of an injury to the SRA is improved by ligation and division of the celiac axis. Options for repair of the SRA include lateral aortorrhapy, patch aortoplasty, resection with end-to-end anastomosis, or resection with interposition grafting with a 12-mm or 14-mm Dacron or PTFE prosthesis. Survival after penetrating wounds of the SRA is 36%, as previously noted, with the combination of injuries to the SRA and inferior vena cava yielding a 100% mortality rate in the recent review from the Ben Taub General Hospital.[12]

TABLE 3. *Operative Management of Retroperitoneal Hematomas After Penetrating Abdominal Trauma**

Location	Approach at Operation
Midline supramesocolic	Open hematoma†
Midline inframesocolic	Open hematoma†
Lateral	
Perirenal	Open hematoma†, unless preoperative CT allows for careful staging of renal parenchymal injury
Paraduodenal	Open hematoma†
Pericolonic	Controversial. No major structures located here, but steady bleeding from lumbar vessels or muscular branches has been a cause of reoperation
Pelvic	Open hematoma†
Portal and retrohepatic	
Portal	Open hematoma†
Retrohepatic	Controversial. Do not open in stable patient if no obvious active hemorrhage after hepatic injury treated

* Modified from Feliciano DV. Abdominal trauma. *In* Schwartz SI, Ellis H, eds. Maingot's Abdominal Operations. East Norwalk, CT: Appleton & Lange, 1989 (publication pending).

† After obtaining proximal and, if possible, distal vascular control.

Proximal vascular control for a penetrating injury to the SMA is obtained through the lateral exposure previously described. Options for repair include lateral arteriorrhaphy, reimplantation, and bypass grafting, remembering the previous suggestion to place the proximal anastomosis of the bypass graft on the distal abdominal aorta away from the pancreas. Survival after wounds of the SMA is 58%; however, this decreases to 22% when any form of repair more complex than lateral arteriorrhaphy is necessary.[68]

Wounds of the proximal left renal artery are easily exposed by the left medial mobilization maneuver. On the right a midline inframesocolic approach with mobilization of the overlying left renal vein allows proximal clamping. Options for repair are discussed in the section on lateral perirenal retroperitoneal hematoma.

A large hematoma at the base of the transverse mesocolon may contain an injury to the superior mesenteric vein. On rare occasions penetrating injuries to this vessel beneath the pancreas may require division of the gland. A significant perforation or transection can be managed by reanastomosis, ligation and saphenous vein grafting to the portal vein, or ligation alone. As with ligation of the portal vein, vigorous infusion of fluids in the early postoperative period is necessary to reverse peripheral hypovolemia.[110] The survival rate after injuries to the superior mesenteric vein the approximately 72%.[3]

Midline Inframesocolic Retroperitoneal Hematoma. Proximal vascular control of the infrarenal abdominal aorta is obtained as previously described, and the repairs used are the same as for the SRA. The survival rate after wounds of the infrarenal aorta is 45%.[117]

Exposure of the infrahepatic inferior vena cava is most complete after the right medial mobilization and Kocher maneuvers illustrated in Figure 9. Vascular control is obtained by application of a partial occlusion clamp, compression with spongesticks proximal and distal to the perforation, or complete cross-clamping around the perforation. Hypotension associated with the latter maneuver may be partially alleviated by the simultaneous application of an infrarenal aortic cross-clamp. Options for repair include lateral venorrhaphy, patch cavoplasty with PTFE, end-to-end anastomosis, or interposition grafting with an externally supported PTFE prosthesis. The survival rate after penetrating wounds of the infrarenal inferior vena cava is 83%.[118] This decreases to 36% with injury to the retrohepatic inferior vena cava, 53% with the suprarenal inferior vena cava, 49% at the level of the renal veins, and 49% at the confluence of the common iliac veins.[118]

Lateral Perirenal Retroperitoneal Hematoma. This should be opened unless preoperative staging by CT documents that a limited renal injury is present.[42,81] Proximal vascular control at the midline is mandatory before the hematoma and kidney are manipulated.[81]

Severely injured kidneys or renal arteries are treated by nephrectomy whenever the patient is hypotensive, has multiple injuries, and the contralateral kidney has a normal appearance on a preoperative or intraoperative IVP. Injuries of the renal vein are treated by lateral venorrhaphy or ligation, as previously noted.

Lateral Paraduodenal Retroperitoneal Hematoma. This hematoma is opened to rule out a perforating injury to the retroperitoneal duodenum, inferior vena cava, or right renal artery. A massive hematoma in this location strongly suggests injury to either the inferior vena cava or right renal artery and is approached by preliminary mobilization of the ascending colon and an extensive Kocher maneuver to expose either vessel. Techniques for repair of the injured duodenum, inferior vena cava, or right renal artery have been discussed previously.

Lateral Pericolonic Retroperitoneal Hematomas. While there are no viscera or major vascular structures here, exploration may be warranted to rule out occult retroperitoneal hemorrhage from a lumbar artery or other muscular branch. The insertion of small right-angle retractors into the tract of a missile through the retroperitoneal muscle should allow for selective clipping or ligation of any bleeding vessel.

Lateral Pelvic Retroperitoneal Hematoma. This hematoma should be opened after obtaining proximal and distal vascular control of the iliac vessels as previously described. An injury to the right common iliac vein may require division of the overlying right common iliac artery and mobilization of the aortic bifurcation to the left for complete exposure.[119] The internal iliac artery is best visualized by passing umbilical tapes or vessel loops around the common and external iliac arteries on one side of the pelvis and lifting them simultaneously. Either internal iliac artery may be ligated and divided to allow for better exposure of an injury to the underlying internal iliac vein.

The iliac arteries can be repaired with lateral arteriorrhaphy, transposition of the ipsilateral internal iliac artery, resection with end-to-end anastomosis, or interposition grafting with a saphenous vein or PTFE prosthesis. Extensive enteric or fecal contamination in the area of a major arterial injury should prompt proximal and distal ligation, ipsilateral four-compartment fasciotomy below the knee, and consideration of an extra-anatomic crossover femerofemoral graft.[3] Injuries to the iliac veins are treated with lateral venorrhaphy or ligation.

Portal and Retrohepatic Retroperitoneal Hematoma

The approach to these hematomas is the same as that previously described for the same hematomas secondary to a blunt injury. A Pringle maneuver is applied and careful dissection is performed to precisely define which structures in the porta hepatis have been injured. Backbleeding may be controlled by having an assistant compress all three structures with a forceps right next to the liver. Repair of the perforated portal vein is accomplished as described previously. Should a penetrating wound in the hepatoduodenal ligament injure the hepatic artery, options for treatment include lateral arteriorrhaphy and other such procedures; however ligation is well tolerated if the portal vein is intact.[93]

In conclusion the management of retroperitoneal hematomas is complex and continues to evolve. Nonoperative and operative approaches for blunt *versus* penetrating hematomas differ considerably in certain locations. The surgeon's approach is dictated by the mechanism of injury, location of the retroperitoneal hematoma, hemodynamic status of the patient, and the presence of associated injuries.

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Tumor Necrosis Factor and Wound Healing

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Tumor necrosis factor alpha (TNF), 1 to 500 ng in saline (PBS) or collagen, was applied to the wounds of normal and Adriamycin-impaired mice and wound disruption strength (WDS) and histology were examined. Also wounded mice were administered TNF 25 to 75 μg/kg IP daily and WDS was determined. Wound histology was examined 6 months after wounding and local TNF application. Local TNF 5 to 500 ng in PBS did not significantly affect WDS. Local TNF 5 to 50 ng in collagen increased WDS 33% to 65% in Adriamycin-impaired animals ($p = 0.05$ to $p < 0.02$). Local TNF 50 to 500 ng in collagen increased WDS 23% to 49% in normal animals ($p = 0.08$ to $p < 0.01$). Adriamycin-impaired animals demonstrated improved wound histology with local TNF in collagen. Systemic TNF did not significantly affect WDS. Local TNF in collagen did not induce histologic pathology at 6 months. TNF may modulate macrophage function and local TNF in collagen can improve WDS in normal and Adriamycin-impaired animals.

TUMOR NECROSIS FACTOR alpha (TNF), a product of activated macrophages, was initially described by Carswell et al.[1] for its ability to induce the necrosis of implantable soft-tissue sarcomas. Since that description TNF has been reported to be a mediator of such diverse processes as cancer cachexia,[2] endotoxic shock,[3] and hematopoiesis.[4] More recently experimental observations suggest that TNF may modulate wound healing; TNF stimulates replication of human diploid fibroblasts,[5] chemotaxis by bovine endothelial cells, and angiogenesis in the rat cornea and chick chorioallantoic membrane.[6] Based on these observations, we examined the effect on wound disruption strength (WDS) of the topical application of recombinant human TNF alpha to both normal and Adriamycin-impaired animals. WDS was also analyzed in normal animals that were administered TNF systemically.

Materials and Methods

Experimental Design

In a series of experiments, groups of 12 mice each were wounded then randomized by body weight to receive locally, in a blinded fashion, PBS, TNF in PBS, collagen, or TNF in collagen. Animals were maintained for 11 days, and were weighed on days 5 and 11 as a measure of clinical health and gross nutritional status. Eleven days after wounding the animals were killed and WDS determined. A second series of experiments were performed in which groups of 12 animals were wounded then received TNF IP for 11 days, at which time they were killed and WDS, splenic weight, white blood cell count, and differential cell count were determined. In a final experiment, groups of 6 animals were randomized, wounded, and received locally nothing, collagen, or TNF in collagen, were maintained for 6 months before being killed, and histologic analysis of their wounds was made.

Mice

Male B6DF1 mice (18 to 20 g; Jackson Labs, Bar Harbour, ME) were acclimatized for at least 1 week in a central animal care facility with a 12-hour light/dark cycle and controlled temperature and humidity. Animals randomized by weight before wounding were housed 12 per cage and given food and water ad libitum.

TNF

Recombinant TNF, with an activity of 1.89×10^7 units and endotoxin level of less than 2.5 EU/mg (LAL), the gift of H. Michael Shepard of Genentech, Inc., S. San Francisco, California, was diluted to the appropriate con-

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centrations in phosphate-buffered saline (PBS) or collagen before use.

Collagen

Modified type I bovine collagen (Zyderm II), gift of the Collagen Corp., Palo Alto, California, was diluted to the appropriate concentration in PBS.

Adriamycin

Adriamycin (Adria Labs, Columbus, OH) was diluted to 2 mg/mL in saline immediately before use and 15 mg/kg or an equal volume of saline was administered to each animal by single intraperitoneal (IP) injection synchronous with wounding.

Wounding Technique

Under ether anesthesia groups of 12 animals each, which received either Adriamycin or an equal volume of saline IP, underwent a 3-cm aseptic surgical incision through their shaved dorsal skin and panniculus carnosus. After wounding and before wound closure with clips, animals were randomized to receive the local application to the cut wound surface of PBS, TNF in PBS, collagen, or TNF in collagen. The skin clips were removed and animals were weighed five days after wounding. The animals were killed on day 11 by ether anesthesia, were weighed, and their pelts were rapidly harvested. Dumbbell-shaped skin strips were cut perpendicularly across the wound and WDS was determined using a tensiometer connected to an X-Y plotter and load transducer *via* Wheatstone bridges. The maximal load required for disruption was recorded *via* a digital readout and load deformation curves were obtained in duplicate fashion for each animal.

Histology

One skin strip per animal was fixed in 10% buffered formaldehyde solution (Anderson Labs, Fort Worth, TX) for at least 24 hours; then six skin strips per group were sectioned and stained with trichrome and hematoxylin and eosin (H&E) stains before examination in a blinded fashion by light microscopy.

Long Term

Four groups of six animals each were wounded as described above and received the local application to the wound of nothing, collagen, 50 ng of TNF in collagen, or 500 ng of TNF in collagen. The animals were observed for 6 months then three animals from each group were killed with ether, their pelts harvested, their wounds examined grossly then fixed in 10% formalin, sectioned, stained, and examined histologically. The remaining three animals per group are being maintained for 1 year before wound analysis.

Systemic TNF

After wounding as above, four groups of eight animals each underwent daily IP injection of 25, 50, or 75 μg/kg of TNF in PBS or an equal volume of PBS for 11 days, were killed with ether, and their pelts were harvested. WDS was determined as above along with tail vein white blood cell count, differential cell count, and splenic weight.

Statistical Analyses

Data was entered into an IBM PC XT (IBM, Boca Raton, FL) and statistical analyses were performed using Duncan's multiple-range method with BMDP statistical software on the University of Vermont Academic Computing Center VAX 8600 system.

Results

The Effect of Local Administration of TNF on Wound Healing in Normal Animals

The local administration of the collagen vehicle alone did not result in any significant difference in WDS when compared to animals that received PBS only when analyzed 11 days after wounding (data not shown).

The local administration of 10, 50, 100, or 500 ng of TNF in PBS to the wounds of normal animals did not result in any significant difference in WDS or body weight when compared to animals that received PBS only when analyzed 11 days after wounding (data not shown).

The administration of 10, 50, 100, or 500 ng of TNF in the collagen vehicle locally to the wounds of normal

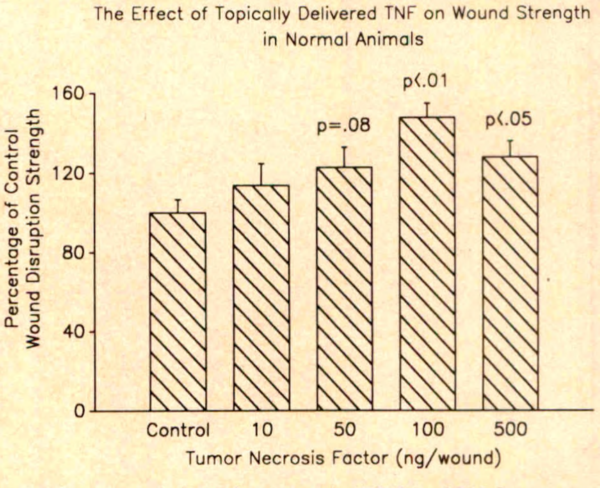

FIG. 1. Mean wound disruption strength (WDS) + SEM for groups of 12 animals each administered TNF locally in collagen in the doses shown expressed as a percentage of the mean WDS of animals administered collagen alone. P values are *versus* collagen-alone control.

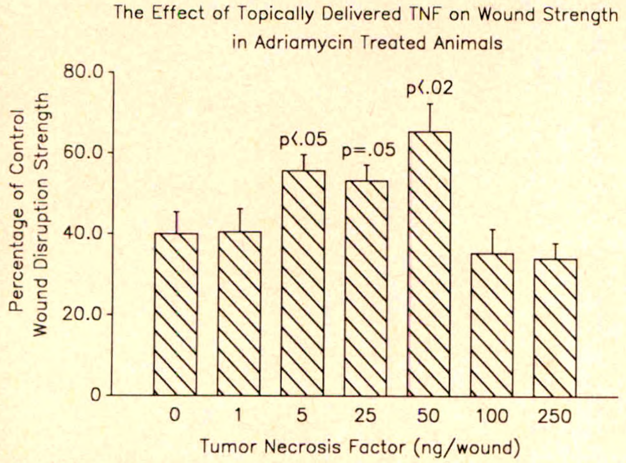

FIG. 2. Mean WDS + SEM for groups of 12 animals each administered Adriamycin 15 mg/kg IP then TNF locally in collagen in the doses shown expressed as a percentage of the mean WDS of animals administered saline IP and collagen alone locally. P values are *versus* animals administered Adriamycin IP and collagen alone locally.

animals resulted in a 14% to 49% increase in WDS 11 days after wounding, as compared to animals that received collagen alone with no significant effect on body weight. This increase was significant in animals that received 50, 100, or 500 ng TNF ($p = 0.08$ to $p < 0.01$; Fig. 1).

Histologic examination failed to reveal any difference in collagen deposition, wound cleft width, or cellular infiltration in the area of the wound cleft in normal animals that received TNF in collagen *versus* normal animals that received collagen only.

The Effect of Local Administration of TNF on Adriamycin-Impaired Wound Healing

After noting an improvement in wound healing in normal animals that received TNF in collagen, we examined the effect of local TNF administration in our model of Adriamycin-impaired wound healing. Animals administered Adriamycin synchronous with wounding typically demonstrated a WDS 60% of normal animals 11 days after wounding. Among animals that received Adriamycin, the local administration of the collagen vehicle alone did not significantly affect WDS (data not shown). Among animals that received Adriamycin, the administration of 10, 50, or 500 ng of TNF in PBS locally to the wound did not significantly affect WDS or body weight (data not shown).

WDS was then assayed in animals that received Adriamycin IP and 1 to 250 ng of TNF applied locally to the wound in the collagen vehicle. Adriamycin animals that

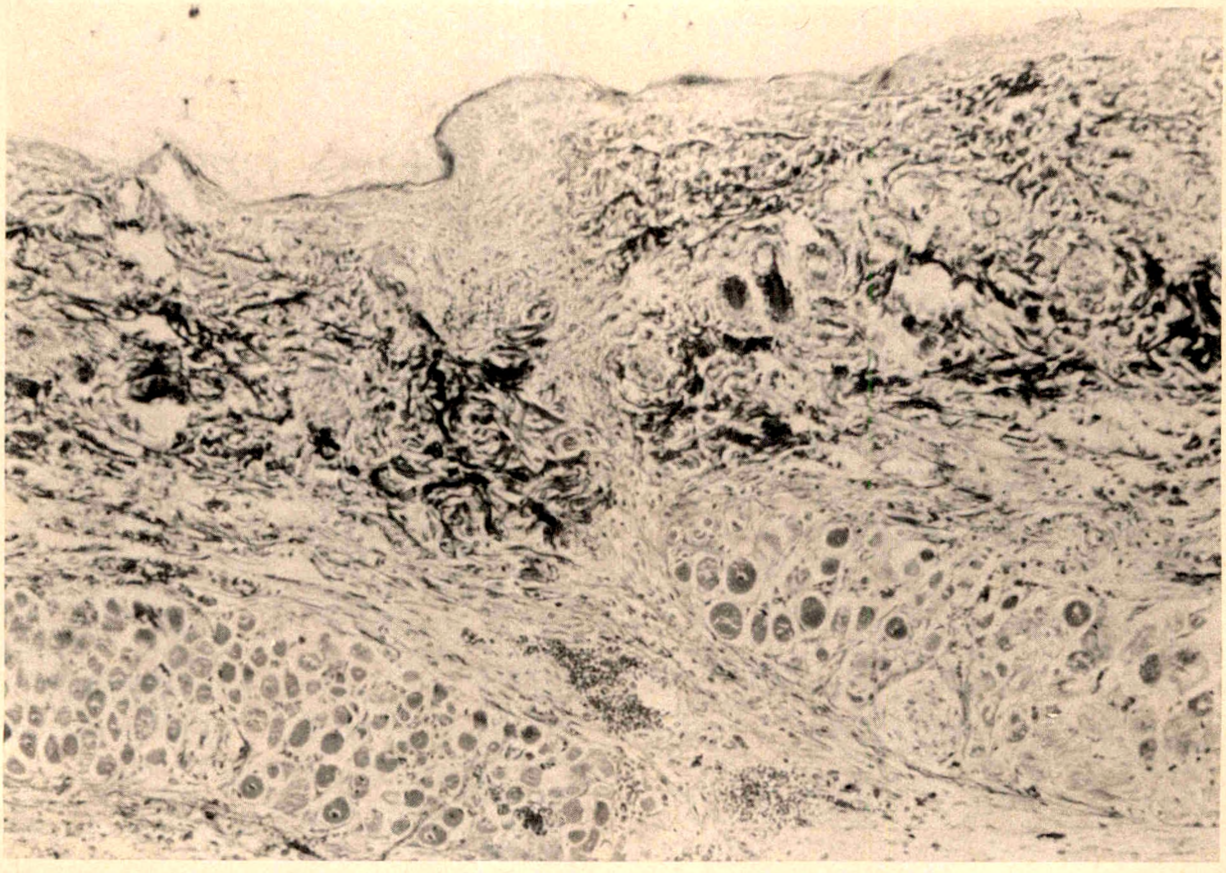

FIG. 3. High-power view of a trichrome-stained wound cleft from a mouse 11 days after wounding and the administration of saline IP and collagen without TNF locally. The wound cleft is narrow and bundles of collagen are noted in the area of the wound.

received 5, 25, or 50 ng of TNF in collagen applied to the wound demonstrated a 33% to 65% increase in WDS as compared to animals which received Adriamycin and collagen alone ($p = 0.05$ to $p < 0.02$), again with no demonstrable effect on body weight. The administration of 1, 100, or 250 ng of TNF in collagen applied to the wound did not significantly affect the WDS (Fig. 2).

Histologic analysis revealed a widened wound cleft and decreased collagen deposition in the wounds of animals administered Adriamycin as compared to normal animals (Figs. 3 and 4). Among animals given Adriamycin, the administration of 1 to 250 ng of TNF in collagen locally to the wound resulted in a narrowed wound cleft and increased collagen deposition in the area of the wound as compared to animals administered collagen alone (Fig. 5).

The Effect of Systemic TNF Administration on Wound Healing

The administration of 25, 50, or 75 μg/kg of TNF IP daily for 11 days to normal animals resulted in a dose-dependent increase in white blood cell count, peripheral monocyte count, and splenic weight, a dose-dependent decrease in peripheral neutrophil count, and no difference in body weight. WDS was nonsignificantly increased in animals that received 25 or 50 μg/kg of TNF and was not affected by the 75 μg/kg dose (Table 1).

Discussion

Impaired wound healing is a significant clinical problem with more than 1 million patients affected annually. The increased incidence of wound complications noted after surgical procedures in a variety of clinical situations including malnutrition, diabetes mellitus, chemotherapy, and radiation therapy, results in increased morbidity and mortality rates. The incidence of wound complications is likely to increase as the patient population ages and procedures and therapies become more complex. The ability to modulate wound healing, particularly in high-risk patients, may reduce the morbidity and mortality associated with surgical procedures.

Macrophages play a critical role in wound healing. Animals depleted of macrophages exhibit impaired wound healing, as do animals administered anti-macrophage antibodies locally to the wound.[7] Moreover substances such as platelet-derived growth factor, Glucan, and transforming growth factor beta, which are macrophage products or act through macrophage stimulation, have previously been demonstrated to modulate wound healing.[8–10] TNF is a ubiquitous inflammatory mediator released by acti-

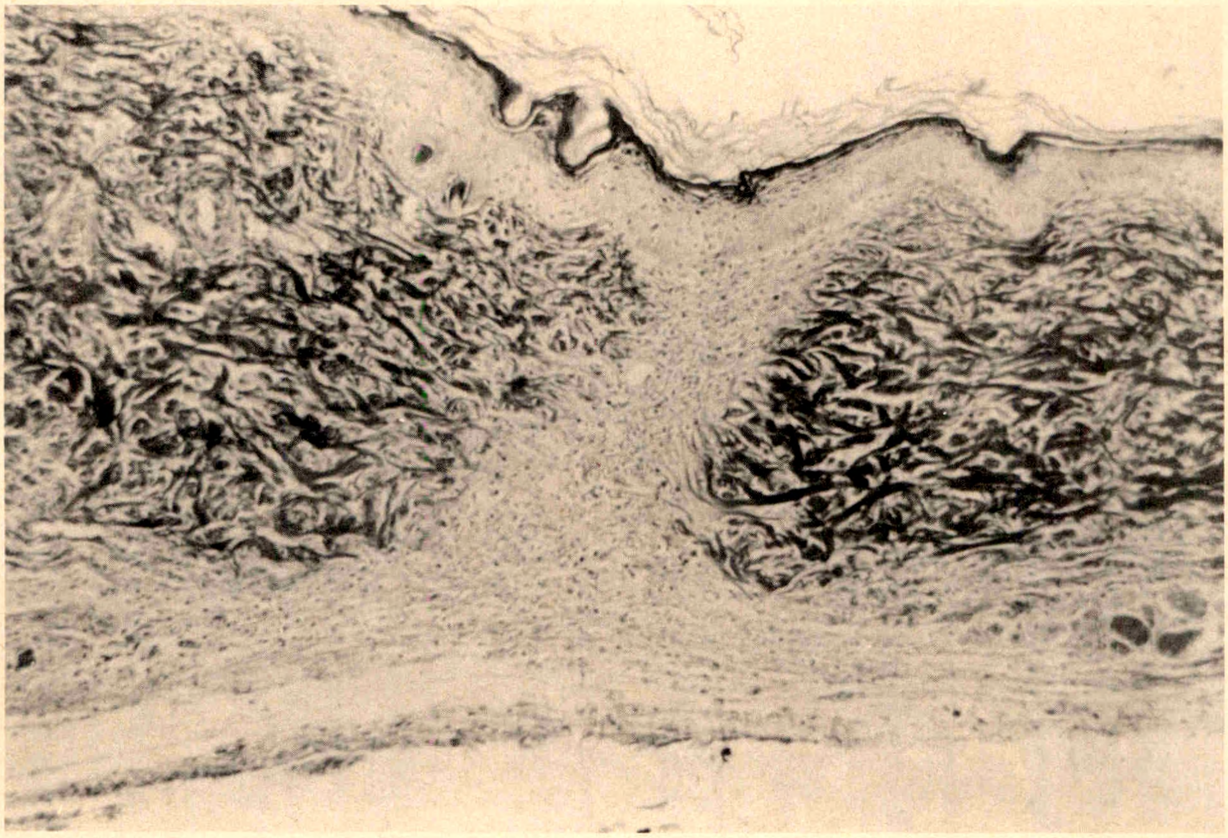

FIG. 4. High-power view of a trichrome-stained wound cleft from a mouse 11 days after wounding and the administration of Adriamycin 15 mg/kg IP and collagen alone locally. The wound cleft is markedly widened and decreased collagen deposition is noted in the area of the wound.

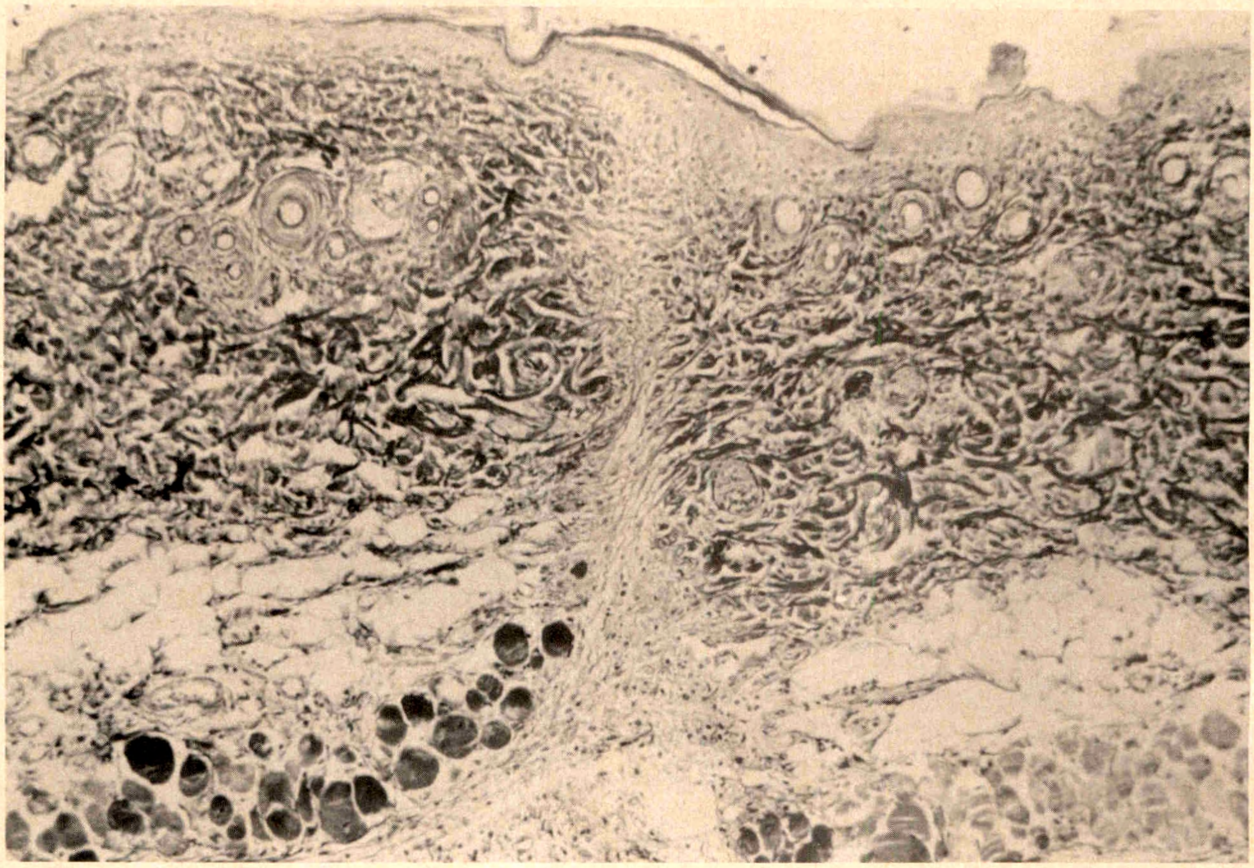

FIG. 5. High-power view of a trichrome-stained wound cleft from a mouse 11 days after wounding and the administration of Adriamycin 15 mg/kg IP and 5 ng of TNF in collagen locally. The wound cleft is narrowed and there is increased collagen deposition in the area of the wound as compared to the animals that received Adriamycin IP and collagen alone locally.

vated macrophages, which induces macrophage release of a variety of factors including macrophage colony-stimulating factor[11] and interleukin-1,[12] and potentiates the macrophage response to other lymphokines.[13] Recombinant TNF is a 17-kD protein with biologic activities similar to the native glycoprotein[14] and demonstrates retained activity across species lines.[15] Secondary to its proposed roles in endotoxic shock[16] and *in vitro* cell culture-growth inhibition,[17] TNF has acquired a negative connotation; however in the appropriate concentration and microenvironment TNF is a potentiator of several biologic processes including hematopoiesis[18] and angiogenesis.[6]

TABLE 1. *Effect of Systemic TNF Administration*

Group	WDS (g)	WBC	PMN	MONO	Splenic Weight (g)
		(10 3rd/mm 3rd)			
Control	112.9	15143	1918	528	88
	6.2	1736	275	106	4.5
25	134.1	12830	1477	2110	84
	8.3	1158	265	464	4.1
50	137.1	18200	1450	2250	94
	12.5	1670	281	432	3.0
75	114.4	19525	963	4063	103
	12.5	1960	150	845	4.2

Mean wound disruption strength (WDS), white blood cell (WBC), monocyte (MONO), and neutrophil (PMN) counts and splenic weights ± SEM of groups of eight mice each administered TNF IP daily in the μg/kg doses shown daily 11 days before assay.

In addition to its effects on the macrophage, TNF acts on other cell types present in the wound. TNF is chemotactic for endothelial cells[6] and induces the formation of capillary tubelike structures in three-dimensional collagen gels.[6] In the rat cornea and the chick chorioallantoic membrane, TNF has direct angiogenic activity[6] that in a healing wound could serve to increase tissue oxygen tension and aid in fibroblast maturation.[19]

To augment wound healing in our model, the dose of TNF used was critical. The local application of TNF resulted in an increased WDS only within a narrow dose range, from 5 to 50 ng, similar to the range found to stimulate angiogenesis *in vitro*.[6] *In vitro* higher concentrations of TNF led to inflammatory changes that may correlate with the failure of the higher doses of TNF used in our studies to significantly affect WDS.

The timing of TNF presence in the wound is also likely to be important. In our model we found that TNF application synchronous with wounding led to an increased

WDS, while Steenfos et al.,[20] examining DNA, hydroxyproline, and protein content in wound chambers in rats, found that the daily application of TNF was slightly inhibitory and prevented the stimulatory effects of transforming growth factor beta. We believe that this highlights the complexity of wound healing processes, the importance of timing in the delivery of growth factors to the wound and the need for immunohistochemical studies to ascertain the timing and location of various factors in the normal and impaired wound.

The timing of TNF release into the wound is dependent on the vehicle used, and in our model, the local administration of TNF to the wound resulted in an increase in WDS only when in a collagen vehicle. TNF administered in PBS may be rapidly degraded, while TNF in collagen may be released more slowly. Although pharmacokinetic studies have not been performed analyzing TNF release from collagen, Sprugel et al.[21] demonstrated that 125I-labeled transforming growth factor beta was released from collagen over several days. In addition collagen may act as a scaffolding for cells migrating into the area of the wound.

TNF significantly affected wound healing when administered locally to the wound but not when administered systemically, despite using doses that significantly increased the white blood cell and monocyte counts and decreased the neutrophil count. This is in contrast to Glucan, a known macrophage stimulant, which has been reported to increase wound healing when administered both locally and systemically.[9]

The local administration of collagen, 50 ng TNF in collagen, or 500 ng TNF in collagen did not result in any gross or histologic wound pathology 6 months after wounding. Wounds healed well without significant scarring and no differences were noted between the groups. The local administration of TNF in a dose ten times that required to affect a significant increase in WDS did not result in any histologic wound pathology.

The studies reported here demonstrate a potentiating effect of TNF in wound healing. Although the precise effects of TNF on wound healing have not been defined, TNF is a modulator of macrophage activity *in vitro* and is likely to be active within the inflammatory milieu of the wound. Macrophage modulation by TNF within the wound represents a theoretical hazard to the proposed clinical administration of anti-TNF antibodies to patients with healing wounds.

Our investigation demonstrated that the local administration of TNF in collagen to the wounds of normal and Adriamycin-impaired mice resulted in an increased WDS and an improved histologic appearance. The repeated systemic administration of TNF had no effect on wound healing in this model over the dose range studied. We have demonstrated that TNF, in the appropriate concentration, timing, and vehicle, modulates wound healing and we hypothesize that TNF is present and active in normal wound-healing processes.

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Tissue Plasminogen Activator Reverses the Deleterious Effect of Infection on Colonic Wound Healing

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Fibrin deposition in response to bacterial peritonitis appears to predispose to residual infection in the peritoneal cavity. Our previous studies have demonstrated that intraperitoneal fibrinolysis using human recombinant tissue plasminogen activator (t-PA) prevented abscess formation in a rat intra-abdominal sepsis model. To investigate the potential adverse side effects of its use in the peritoneal cavity, the effect of t-PA on colonic anastomotic wound healing and on systemic coagulation parameters was examined in the rat. T-PA did not adversely affect colonic healing five and ten days after anastomosis. In animals infected intraperitoneally at the time of the anastomosis, t-PA reversed the inhibition of healing induced by perianastomotic abscesses at five days. This effect was mediated by the ability of t-PA to prevent perianastomotic abscess formation. After intraperitoneal administration, t-PA had no effect on prothrombin and partial thromboplastin times in either uninfected or infected animals and there was no evidence of clinical bleeding related to its use. These studies suggest that intraperitoneal fibrinolysis using t-PA may provide a safe, effective form of adjuvant therapy in the management of fibrinopurulent peritonitis.

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THREE MAJOR LOCAL mechanisms of bacterial clearance are initiated in response to bacterial soiling of the peritoneal cavity.[1] These include (1) mechanical clearance of bacteria *via* the diaphragmatic lymphatics, (2) phagocytic uptake and killing of bacteria after the influx of phagocytic cells into the peritoneal cavity, and (3) sequestration of bacteria within fibrinous exudates. Fibrin deposition initially retards the spread of bacteria across the peritoneal cavity and into the systemic circulation.[2] Teleologically this phenomenon may have served a beneficial role in that it reduced the magnitude of the potentially life-threatening bacteremia. However data derived from both *in vitro* and *in vivo* studies suggest that bacterial sequestration within fibrinous exudates may also predispose to abscess formation, thereby representing an undesirable side effect of normal host defense mechanisms. Fibrin matrices have been shown to impair the phagocytic killing of bacteria by neutrophils[3] and to impede macrophage migration.[4] Impairment of phagocytic cell function would presumably encourage residual infection. Evidence for the role of fibrin in the pathogenesis of abscesses has also been derived from *in vivo* studies. Prevention of fibrin deposition using anticoagulants[5–7] or direct fibrinolysis with fibrinolytic agents[8] has been shown to prevent abscess formation in a variety of intra-abdominal infection models.

Previous studies from our laboratory have demonstrated that intraperitoneal (IP) fibrinolysis using recombinant tissue plasminogen activator (t-PA) obviated subsequent IP abscess formation in the rat fibrin clot intra-abdominal infection model. Several other issues must be addressed before considering t-PA for use in the clinical setting. These include the effect of t-PA on intestinal anastomotic wound healing, the potential bleeding complications related to the presence of a fresh anastomotic wound and a raw granulating surface, and finally, its effect on parameters of systemic coagulation, which may result in complications when associated with major surgery. While the bleeding complications associated with intravenous administration of t-PA are well documented,[9,10] the effects of t-PA after IP administration on coagulation parameters are unknown. In addition the effect of t-PA on wound healing is poorly defined. One might speculate that t-PA may interfere with wound healing by lysing the fibrin matrix on which cells migrate into a healing wound.[11] Conversely fibrinopeptides released from fibrinogen by t-PA[12] as well as fibrin degradation products

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resulting from the effect of plasmin on fibrin are well-known chemoattractants[13,14] and may enhance wound healing.

The purpose of these studies was to determine the effect of IP administration of t-PA on colonic anastomotic wound healing. Furthermore because infection in the perianastomotic region has been shown to impair healing, we hypothesized that infection prevention using t-PA might reverse the infection-induced impairment in anastomotic wound healing.

Materials and Methods

Bacterial Strains and Growth Conditions

Escherichia coli strain 00 was a clinical isolate from the University of Minnesota Hospitals (Minneapolis). *Bacteroides fragilis* strain VPI 9032 was obtained from Dr. Tracy D. Wilkins, Virginia Polytechnic Institute and State University (VPI; Blacksburg, VA). Growth conditions and methods of preparation and enumeration have previously been described for both bacterial species.[3,15]

Animal Model of Colonic Anastomotic Healing

Male Wistar rats (200 to 225 g) were anesthetize using a halothane-nitrous oxide-oxygen mixture. *Via* a midline laparotomy incision, the sigmoid colon 1 cm above the pelvic brim was isolated and divided using scissors. A single-layer end-to-end anastomosis was performed using eight interrupted 6–0 polypropylene stitches (Prolene, Ethicon Corp., Toronto, Canada). After the anastomosis animals were randomly assigned to one of four groups: (I) IP lavage with 4 mL of Hanks' balanced salt solution (HBSS); (II) IP lavage with 4 mL of t-PA 0.01 mg/mL; (III) IP lavage with 4 mL of HBSS plus IP inoculation of an infected fibrin mesh at the anastomotic site; (IV) IP lavage with 4 mL of t-PA plus IP inoculation of an infected fibrin mesh at the anastomotic site.

After surgery all animals received a single intramuscular injection of gentamicin (30 mg/kg) plus clindamycin (110 mg/kg) and also a subcutaneous injection of 10 mL of sterile saline. Human recombinant t-PA was donated by Dr. John Kaumeyer (Genentech, South San Francisco, CA). The dosage of t-PA used was based on its efficacy in abscess prevention in previous studies

At days 5 and 10 animals were killed by carbon dioxide asphyxiation. The peritoneal cavity was inspected for the presence of abscesses and the anastomosis was assessed for bursting pressure and perianastomotic abscess formation. A sample of colon, measuring 1 cm in length (0.5 cm on each side of the anastomosis) was excised and used for determination of hydroxyproline content.

Anastomotic Bursting Pressure

The anastomotic bursting pressure (ABP) was measured *in situ* with sutures and adhesions left in place.[16] The colon was ligated at the peritoneal reflection distal to the anastomosis and air was insufflated into the descending colon *via* an incision just distal to the splenic flexure. Air was insufflated at a constant rate of 2 mL per minute using a Harvard pump (Harvard Apparatus, Infusion/Withdrawal Pump, Model 944, South Natick, MA). ABP was defined as the pressure at which air first leaked from the segment. This was determined using a sidearm attachment to a mercury manometer.

Hydroxyproline Content

Collagen content was estimated by measurement of the hydroxyproline content using the modified method of Woessner.[17,18] Briefly, the excised colon was washed with saline and lyophilized. A 10-mg sample of lyophilized tissue was subjected to acid hydrolysis for 16 hours at 120 C. After neutralization, the hydrolysates were oxidized at room temperature for 20 minutes. The oxidation products of proline were extracted with toluene and the remaining aqueous solution was boiled at 100 C for 30 minutes to convert the oxidation products of hydroxyproline to pyrrol. The pyrrol was then extracted with toluene and mixed with Ehrlich's reagents. The samples were read at 560 nm and quantitated by comparison to a standard curve using hydroxyproline standards (Sigma Chemical Co., St. Louis, MO). Results are expressed as ug hydroxyproline per mg dry tissue.

Formation of the Infected Fibrin Mesh

E. coli 2×10^7 cfu and *B. fragilis* 2×10^9 cfu were mixed with sterile human fibrinogen (100 mg/dL, Sigma[19]) in a 12 × 75 mm polystyrene tube and clotting was initiated with thrombin (Parke-Davis, Morris Plains, NJ; final concentration, 3 IU/mL). Before the clot became fully polymerized, the mixture (2 mL) was drawn up into a sterile 10-mL pipette and inoculated into the left lower quadrant of the peritoneal cavity at the site of the anastomosis, where final clot polymerization occurred. This model was intended to mimic the clinical setting of localized infection at the anastomotic site.

Systemic Effect of T-PA

In a separate group of animals, not undergoing colonic anastomosis, the systemic effect of IP t-PA was investigated. Animals were assigned to an uninfected group or a group inoculated IP with an infected fibrin clot and were lavaged IP with 4 mL of either HBSS or t-PA (0.01 mg/mL). At t = 0, 1, 2, 4, and 18 hours, blood was drawn for measurement of t-PA and fibrinogen as well as the prothrombin and partial thromboplastin time. To obviate *in vitro* activity of t-PA, D-Phe-Pro-Arg-chloromethylketone (2.4 mM) was added to inhibit t-PA activity.[20] t-PA was measured by an amidolytic method with the synthetic substrate S-2288 (Kabi Diagnostics).[20] Amidolytic activity was determined spectrophotometrically as a change in optical density after a 2.5-hour incubation. The prothrombin (PT) and partial thromboplastin (PTT) times were determined in the clinical laboratory at the Toronto General Hospital.

Statistics

Data were analyzed using a one-way analysis of variance and multiple comparisons between groups were performed using Duncan's Multiple Range Test. Differences in hydroxyproline content between day 5 and day 10 were determined using a Student's t test. The rate of abscess formation was compared using Fisher's exact test. Results are expressed as mean and standard errors.

Results

Animal Welfare

All animals survived surgery and recovered from anesthesia five to ten minutes after being returned to their cages. Overall mortality rate was 1.8% (2 of 113 animals). Both animals died on day 3 from sepsis due to diffuse peritonitis. Among the survivors, animals generally lost weight for the first 48 hours. By the time of sacrifice, 92% of animals had either surpassed their initial weight or were gaining weight.

Anastomotic Bursting Pressure (Fig. 1)

Colonic bursting pressure was assessed five and ten days after operation. By postoperative day 5 the ABP in control animals was 117 ± 7 mmHg (n = 25), with 96% bursting at the anastomotic site. Intraperitoneal lavage with t-PA at the time of surgery had no effect on the ABP (117 ± 10 mmHg, n = 15) compared to control animals. The colon burst at the anastomotic site in 80%. Inoculation of an infected *E. coli-B. fragilis* fibrin mesh at the time of surgery caused a significant reduction in ABP (63 ± 10, n = 15) and all colons burst at the anastomotic site. The simultaneous instillation of t-PA with IP inoculation of an *E. coli-B. fragilis* fibrin mesh caused the return of the colonic bursting pressure to control levels (118 ± 9 mmHg, n = 15). The anastomosis was the site of bursting in 87% of animals.

By postoperative day 10, the ABP in all groups had significantly increased from day 5. However the ABPs did not differ among groups. The site of bursting was away from the anastomosis in > 80% of animals in each group.

Abscess Formation (Fig. 2)

At 5 days peritoneal lavage with t-PA did not increase the rate of perianastomotic abscess formation compared to lavage with HBSS (20% *vs.* 24%, respectively) in uninfected animals. However inoculation of the peritoneal cavity with an infected fibrin mesh at the time of surgery caused abscess formation in all animals. This increased rate of abscess formation was prevented by simultaneous peritoneal lavage with t-PA, a finding confirming previous studies performed in a model in which no anastomosis was performed. Because perianastomotic infection has been shown to be associated with impaired anastomotic wound healing,[21] it was hypothesized that peritoneal lavage with t-PA in animals infected IP with an *E. coli-B. fragilis* fibrin mesh might obviate abscess formation and reverse the effect of infection on wound healing. This hypothesis was supported by the findings that t-PA reduced abscess formation from 100% to 19% and its use was associated with an improvement in mean ABP from 63 ± 10 mmHg to 118 ± 9 mmHg. Further support for the concept that reduced ABP was related to the presence of local infection was obtained by correlating ABP with the presence or absence of abscesses within each group and for all animals studied. In animals with abscesses, the ABP was significantly lower than in animals without abscesses

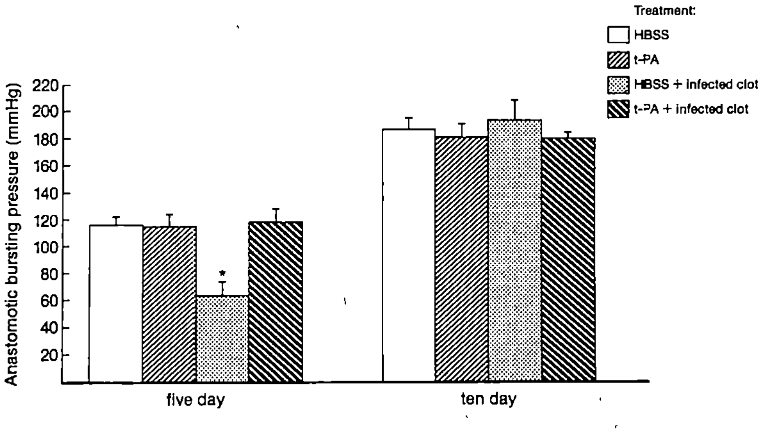

FIG. 1. Effect of t-PA and perianastomotic infection on anastomotic-bursting pressure. Data are expressed as the mean and standard error of bursting pressures measured in 15 to 25 animals per group at day 5 and 8 to 10 animals per group at day 10. *p < 0.05 *versus* HBSS alone and t-PA + infected clot.

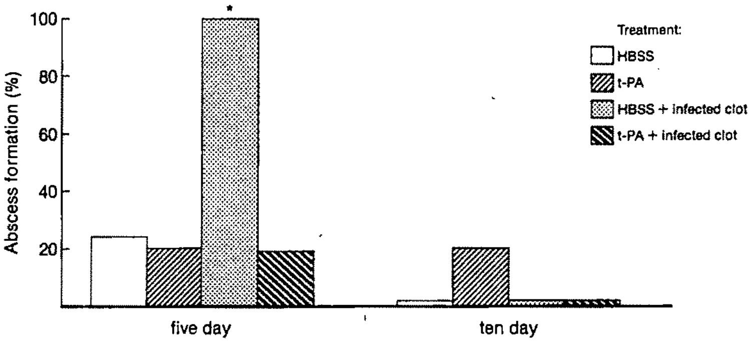

FIG. 2. Effect of various treatment regimens on perianastomotic abscess formation. Data are expressed as the mean and standard error of the rate of abscess formation in each treatment group. *p < 0.0001 *versus* HBSS alone and t-PA + infected clot.

(63 ± 6 mmHg, n = 27 *vs.* 132 ± 4 mmHg n = 44 respectively, p < 0.0001, Student's t test). A similar pattern was noted within each group.

By day 10 the rate of abscess formation was reduced in all groups. Abscesses were rarely found and the rate did not differ between groups.

Hydroxyproline Content (Table 1)

To confirm that reduced ABP reflected impaired wound healing, collagen content at the perianastomotic site as estimated by hydroxyproline was measured. At day 5 anastomotic hydroxyproline was significantly lower in animals inoculated IP with an infected fibrin clot than in control animals. As noted for ABP, peritoneal lavage reversed the inhibitory effect of infection on anastomotic hydroxyproline content. Hydroxyproline content in animals lavaged IP with t-PA did not differ from control.

By day 10 anastomotic hydroxyproline content was increased compared to day 5 levels and did not differ among groups. These findings are consistent with the high ABP in all groups and the low rate of perianastomotic abscesses observed in all groups.

Coagulation Parameters

There was no gross evidence of bleeding in any animal. In uninfected animals (Table 2), peritoneal lavage with t-PA resulted in an increase of systemic t-PA levels from barely detectable to a peak at one hour of 9.0 ± 2.1 ng/mL. One indicator of the systemic activity of t-PA is a reduction of plasma fibrinogen due to the fibrinogenolytic activity of t-PA. The fibrinogen level in t-PA-treated uninfected animals fell by approximately 20%, but remained within the normal range.

In infected animals treated IP with HBSS, no increase in systemic t-PA occurred. In t-PA-treated infected animals (Table 3), systemic t-PA levels increased and did so to a greater extent than in uninfected animals receiving t-PA (Table 2). As expected after acute infection, fibrinogen levels were increased. This increase was transiently reduced in animals treated with IP t-PA. However by 4 hours fibrinogen levels in t-PA-treated animals did not differ from control. In infected animals PT and PTT remained within the normal range in both HBSS- and t-PA-treated animals (data not shown).

Discussion

Fibrin deposition in response to peritoneal infection plays a crucial role in sequestering and walling off bacteria locally within the peritoneal cavity.[2] Previous studies from our laboratory have demonstrated the efficacy of the fibrinolytic agent, tissue plasminogen activator, in preventing intra-abdominal abscess formation.[8] This suggested its potential use as an adjunct to surgery and antibiotics in the management of diffuse fibrinopurulent peritonitis, a setting in which postoperative abscess formation is relatively common.

TABLE 1. *Anastomotic Hydroxyproline Content*

	Hydroxyproline Content (μg/mg dry weight)	
Group	5 days	10 days
HBSS	10.1 ± 0.6	14.2 ± 0.6‡
HBSS + clot	8.4 ± 0.5†	14.4 ± 0.8‡
T-PA	10.4 ± 0.4	14.2 ± 0.6‡
T-PA + clot	9.7 ± 0.6	14.8 ± 0.6‡

* n = 16 per group, mean ± standard error.
† p < 0.05 *versus* HBSS control.
‡ p < 0.01 *versus* same group at day 5.

TABLE 2. *Systemic Effects of T-PA in Uninfected Animals**

Time (hours)	Fibrinogen (mg/dL)	T-PA (ng/mL)
0	179 ± 15	0.5 ± 0.3
1	139 ± 4	9.1 ± 2.1†
2	134 ± 7	10.0 ± 3.6†
4	209 ± 24	1.3 ± 0.4
18	228 ± 9†	0.9 ± 0.4

* Data expressed as mean ± standard error, n = 4 to 6 per group.
† p < 0.05 *vs.* time = 0.

TABLE 3. *Systemic Effects of T-PA in Animals Infected Intraperitoneally*

Time (hours)	Fibrinogen (mg/dL)		T-PA (ng/mL)	
	HBSS	T-PA	HBSS	T-PA
0	156 ± 13		2.1 ± 2.1	
1	225 ± 21	ND	0.2 ± 0.2	ND
2	180 ± 23	140 ± 14	1.5 ± 1.5	28.5 ± 8.0†
4	178 ± 7	191 ± 14	0.2 ± 0.2	8.4 ± 4.3
18	246 ± 65	213 ± 56	0.9 ± 0.6	0.6 ± 0.3

* All animals were infected intraperitoneally and then treated by lavage with either HBSS or t-PA. Data are expressed as mean ± standard error; n = 4 per group.

† $p < 0.05$ *vs* time = 0.

ND, not determined.

Because fibrin deposition, as an integral part of the inflammatory response, has been considered an important element of normal wound healing, the possibility that fibrinolysis may be detrimental to anastomotic healing was considered. The present studies demonstrated that peritoneal lavage with t-PA at the time of colonic anastomosis had no deleterious effect on ABP or collagen deposition at the anastomotic site. These results suggest that either fibrinolysis *per se* has no adverse effect on wound healing or that the degree of fibrinolysis mediated by the dose of t-PA used in these studies (0.01 mg/mL) was insufficient to impair wound healing. One further alternative is that human t-PA was unable to effect fibrinolysis in the rat due to species differences. Several lines of evidence make this last possibility unlikely. First t-PA reduced systemic fibrinogen levels, indicating its ability to act directly on rat fibrinogen. Second t-PA prevented abscess formation in the gelatin capsule peritonitis model in the rat,[8] where only native rat fibrin and plasminogen are present. Finally t-PA prevented abscess formation in the fibrin clot model, when the fibrinogen used was plasminogen-free (unpublished observation). Thus lysis was mediated by rat plasmin, generated by the action of human t-PA on rat plasminogen. Together these data indicate that human recombinant t-PA is capable of lysing rat fibrin in rats *via* an effect on rat plasminogen.

Perianastomotic infection has been associated with impaired anastomotic healing in both clinical and experimental studies. Schrock et al.[22] demonstrated that anastomotic dehiscence occurred in 10.5% of cases when peritonitis, abscess, or fistula was present at operation compared with 3.7% when no infection was present. In experimental models, anastomoses performed in the presence of local infection also demonstrated reduced anastomotic strength.[21] This reduction correlated with a decrease in collagen content at the anastomotic site. In accordance with these findings, the present studies demonstrated that at five days animals inoculated locally with an infected fibrin mesh had reduced ABP compared to controls. This reduction was also reflected in the depressed collagen content at the anastomosis. By day 10 ABP in animals infected at the time of surgery was comparable to control animals. A similar example of the ability of local infection to delay, rather than prevent, healing has been previously demonstrated by Yamakawa et al.[23] using a dog model of diverticulitis.

Peritoneal lavage with t-PA in animals infected with *E. coli-B. fragilis* fibrin mesh restored ABP to control levels at five days. The most likely explanation for this effect was the ability of t-PA to prevent local infection. Indeed when all animals were considered, the presence of local infection was associated with a significantly reduced ABP. Based on studies showing that local infection promotes collagenolysis at the anastomotic site,[21] one might speculate that the improved healing effected by t-PA was due to the clearance of local infection and the resultant reversal of the collagenolytic activity. Studies examining collagen turnover at the anastomotic site would address this question. These present studies do not rule out the possibility that t-PA caused its beneficial effect through other mechanisms such as the release of chemoattractant fibrinopeptides or fibrin degradation products, the action of its homologous Epidermal Growth Factor sequence[24] on host cells, or a direct stimulatory effect on host defense mechanisms. All such mechanisms would promote healing, either directly or indirectly, independent of the clearance of bacteria by local fibrinolysis.

Bleeding complications after intravenous administration of t-PA are caused by a combination of the lysis of hemostatic plugs as well as defects in coagulation.[25] In the present studies, no evidence of gross bleeding was noted after intraperitoneal administration of t-PA in either uninfected or infected animals. In uninfected animals, there was a small transient increase in plasma t-PA levels. This correlated with a small reduction (~ 20%) in fibrinogen levels. However PT and PTT remained normal. In infected animals, systemic t-PA levels were increased to a greater extent after t-PA administration. This was not due to an increased baseline caused by infection because infected animals treated IP with HBSS had undetectable t-PA levels. Rather this likely represents increased permeability of the peritoneum to proteins in the setting of infection. Fibrinogen levels in infected animals was increased compared to uninfected controls, a finding compatible with the acute-phase response to inflammation.[26] T-PA administration, as in uninfected animals, caused a small but transient reduction in these levels. However, despite this evidence of systemic activity of t-PA, the standard coagulation parameters, *i.e.*, PT, PTT remained normal.

The results of these studies suggest that topical application of t-PA in the peritoneal cavity effectively lyses infected fibrin matrices but does not sufficiently disrupt hemostatic plugs from the cut surface of an anastomosis to cause clinical bleeding. In addition the small amount that enters the systemic circulation is insufficient to significantly alter coagulation parameters or cause clinical bleeding from cut surfaces. The explanation for the differential effect between fibrin in the peritoneal cavity and that present in hemostatic plugs at anastomotic sites is unclear. Whether this is due to the fact that hemostatic plugs tend to be more resistant to lysis than an inoculated fibrin mesh due to clot impaction and alpha-chain crosslinking requires further study.[25,27]

Based on studies within this model system, t-PA does not adversely affect anastomotic wound healing and, in fact, may improve healing by enhancing the clearance of local infection. These findings suggest that controlled fibrinolysis using t-PA may be a useful adjunct to surgery and antibiotics in the management of fibrinopurulent peritonitis. Furthermore they suggest the possibility that t-PA may enhance the safety of primary anastomosis in this clinical setting.

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Acute Effect of Experimental Truncal Vagotomy on Serum Gastrin Concentrations

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We studied the acute effect of transthoracic truncal vagotomy or sham vagotomy (control) on fasting serum gastrin concentrations in 22 gastric fistula dogs. A significant ($p < 0.05$) decrease in serum gastrin concentration was detectable within 2.5 minutes after truncal vagotomy, and by 120 minutes serum gastrin has decreased to 15 ± 1 pg/mL in the vagotomy group compared to 28 ± 3 pg/mL in the control group ($p < 0.001$). However by 24 hours after vagotomy, when maximal acid output was reduced by approximately 50%, fasting serum gastrin had increased nearly twofold above control levels in the vagotomy group ($p = 0.06$) and this increase persisted at day 7 ($p < 0.05$). Thus truncal vagotomy had a biphasic effect on serum gastrin concentrations in dogs (acute inhibition followed by stimulation). While the mechanism for the acute fall in gastrin is probably an acute denervation of postganglionic neurons that innervate gastrin cells, the mechanism for the subsequent rise in serum gastrin remains uncertain.

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ACUTE VAGAL ACTIVATION by electrical stimulation,[1] sham feeding,[2,3] insulin-induced hypoglycemia,[3,4] or 2-deoxyglucose infusion[5,6] increases serum gastrin concentrations in dogs. If efferent vagal fibers augment gastrin release, it has been difficult to reconcile the observation that truncal vagotomy (TV) increases, rather than reduces, serum gastrin concentrations in dogs.[7] The increase in serum gastrin after TV is probably due to denervation of the fundus rather than the antrum because proximal gastric vagotomy (PGV) also increases serum gastrin levels,[4,5] while antral vagotomy has no effect on serum gastrin.[3,4,8] However all studies evaluating the effect of vagotomy on serum gastrin in dogs have examined serum gastrin concentrations one day to several years after vagotomy.[3-5,7,8] The acute effect of vagotomy on serum gastrin concentration has not been studied. We hypothesized that acute interruption of the vagal innervation of the stomach might lower serum gastrin concentrations temporarily, followed ultimately by hypergastrinemia. The purpose of this study was to test this hypothesis in gastric fistula dogs.

Materials and Methods

Animal Preparation and Experimental Protocol

Twenty-two mongrel dogs varying in weight from 21 to 33 kg (mean, 26 kg) were studied. Laparotomy was performed at least 3 weeks before experimentation, at which time a gastric fistula drained by a Thomas cannula was placed in the fundus along the greater curvature well above the oxyntic-antral junction. At the same time, pyloromyotomy was performed as a gastric drainage procedure. Animals were fasted for 16 hours before experimentation. Studies were approved by an animal welfare committee.

On three separate days before surgery, two fasting blood samples were obtained 15 minutes apart for measurement of serum gastrin concentration. In addition on each day we measured from the gastric fistula both basal acid output (BAO) for two 15-minute periods and then maximal acid output (MAO) in response to a maximally effective dose of pentagastrin (16 μg/kg/hr i.v.) for eight 15-minute pe-

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riods, as described previously.[9] Gastric juice pH was measured with a glass electrode and converted to hydrogen ion concentration using standard tables, while gastric juice volume was measured in a cylinder to the nearest 0.5 mL.[9] BAO was defined as the sum of the two 15-minute outputs (volume × [H^+]), multiplied by 2 to express results in mmol/hr. MAO was defined as the sum of the four highest 15-minute outputs during pentagastrin infusion.

Dogs were then randomly divided into two groups of 11 dogs each, fasted overnight, sedated with 30 mg/kg pentobarbital intravenously, and then subjected to left thoracotomy under halothane anesthesia given by inhalation. Group A had TV while Group B had sham vagotomy (SV). For TV vagal trunks were identified and isolated before transection of any fibers. Vagotomy *per se* required 30 to 60 seconds to complete. The vagal trunks were tied off proximally and distally, and then transected, with 1-to-2-cm segments of nerve excised. For SV vagal fibers were identified and isolated, but not transected. After TV or SV, a 16F Foley catheter was inserted into the left pleural cavity and placed on suction to re-expand the left lung. This catheter was subsequently removed during wound closure. Surgery was completed within 15 to 25 minutes after TV or SV. Serum gastrin was measured 5 minutes, 2.5 minutes, and immediately before TV or SV, and then 2.5, 5, 10, 30, 60, 120 minutes, and 24 hours after TV or SV. To prevent gastric distention, all dogs had their fistulae left open for at least three hours after operation (or until they were fully alert and standing). In ten animals (five randomly selected from each group), BAO and MAO also were measured at 24 hours. In all 22 animals, basal serum gastrin as well as BAO and MAO were measured on postoperative day 7.

In each dog in the TV group, complete vagotomy was documented by insulin hypoglycemia testing, while in each dog in the sham vagotomy group the postoperative acid secretory response to insulin-induced hypoglycemia was normal.[10]

Serum Gastrin Assay

Serum samples were coded and then assayed for gastrinlike immunoreactivity using antibody 1611.[11] This antibody reacts equally with G17 and G34 and does not crossreact with cholecystokinin. The minimum detection limit of this assay is 0.5 fmol/mL with inter- and intra-assay coefficient of variation of approximately 10% and 5%, respectively.[11] In these 22 dogs, the variation in duplicate basal samples obtained 5 minutes and 2.5 minutes before TV or SV was 10.5% (range, 0 to 25.4%).

Statistics

Student's group t tests were used for comparison of mean gastrin and acid secretion results in vagotomy *versus* control groups. pH values were expressed as medians and tested for significance by the median test. P values < 0.05 were considered significant.

Results

Serum Gastrin Concentration

On the three preoperative study days, mean (± SE) basal serum gastrin concentrations ranged from 24 ± 2 to 27 ± 3 pg/mL in the SV group and from 25 ± 2 to 27 ± 3 pg/mL in the TV group. On the day of surgery, basal serum gastrin levels 5 minutes, 2.5 minutes, and just before truncal or sham vagotomy were similar to these earlier preoperative basal gastrin levels, averaging 25 ± 2 pg/mL in the SV group and 22 ± 2 pg/mL in the TV group. As shown in Figure 1, there was little change in serum gastrin levels during the 120-minute period after SV. However after TV there was an immediate and significant decrease

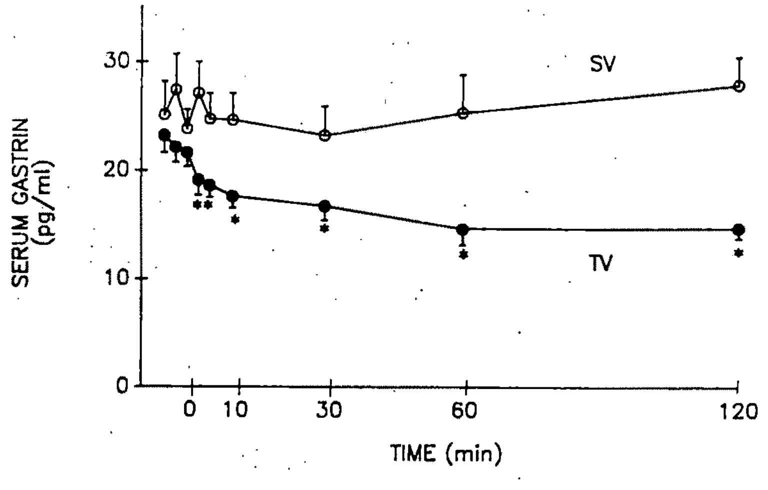


FIG. 1. Effect of truncal vagotomy (TV, n = 11) or sham vagotomy (SV, n = 11) on mean (± SE) serum gastrin concentrations. TV or SV was performed at 0 min. Significant differences ($p < 0.05$) are shown as *.

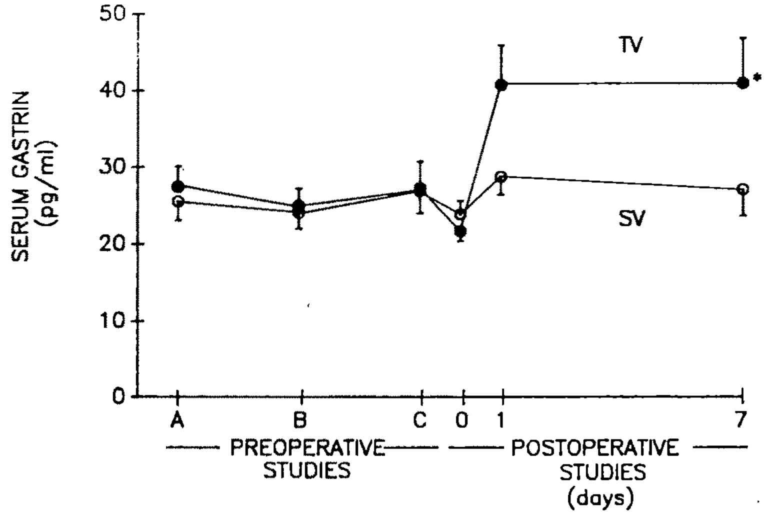


FIG. 2. Effect of truncal vagotomy (TV, n = 11) or sham vagotomy (SV, n = 11) on mean (± SE) serum gastrin concentrations. Preoperative studies (A, B, and C) are shown. TV or SV was performed on day 0. Significant difference ($p < 0.05$) is shown as *.

in serum gastrin below basal serum gastrin levels ($p < 0.05$) and also below gastrin levels in the SV group ($p < 0.05$; Fig. 1). By 120 minutes serum gastrin averaged 28 ± 3 pg/mL in the SV group and 15 ± 1 pg/mL in the TV group ($p < 0.001$), a decrease of nearly 50%.

Within 24 hours after TV, serum gastrin had increased nearly twofold, although this did not quite reach significance ($p = 0.06$) compared to the SV group (Fig. 2). By day 7 serum gastrin averaged 41 ± 6 pg/mL in the TV group and 27 ± 4 pg/mL in control animals ($p < 0.05$; Fig. 2), an increase of approximately 50%.

Acid Secretion

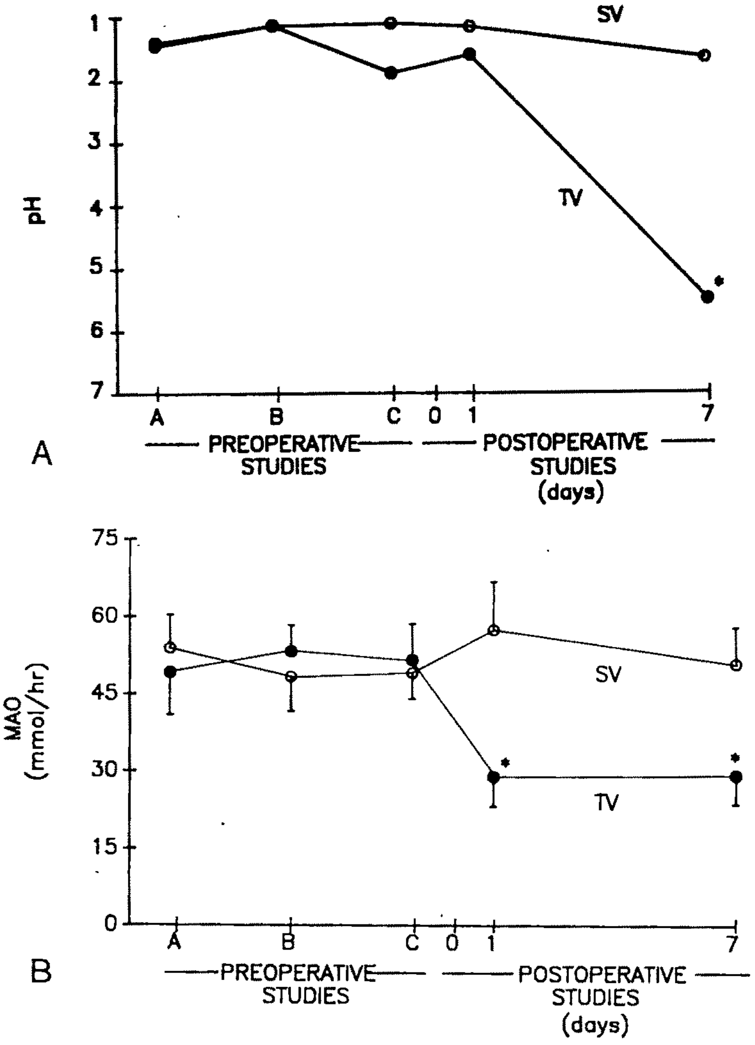
On the three preoperative study days, mean (± SE) basal acid output (BAO) ranged from 1.4 ± 0.6 to 2.8 ± 1.4 mmol/hr in the SV group and from 2.0 ± 1.0 to 3.2 ± 1.8 mmol/hr in the TV group. Although BAO tended to decrease after thoracotomy in both groups, there were no significant differences in postoperative BAO between the SV or TV groups at days 1 or 7. As shown in Figure 3A, median gastric pH was between 1 and 2 before the operation. Median pH was similar on postoperative day 1 in the 2 groups, but was significantly higher on postoperative day 7 in the TV group ($p < 0.05$).

Prevagotomy mean (± SE) maximal acid outputs (MAO) for the TV and SV groups were not significantly different, with an average of approximately 50 mmol/hr (Fig. 3B). MAO was unaffected by SV, while MAO after TV decreased by nearly 50% on days 1 and 7 when compared to the SV group ($p < 0.05$).

Discussion

Several studies in dogs have shown that acute activation of the efferent vagus by electrical stimulation,[1] sham feeding,[2,3] hypoglycemia,[3,4] or 2-deoxyglucose infusion[5,6] increases serum gastrin concentrations promptly. This release of gastrin is prevented by antral vagotomy,[3,4] whereas it is resistant to blockade by atropine.[12] Furthermore cholinomimetic agents are only weak stimulants of gastrin release in dogs.[6] Thus the postganglionic neurotransmitter responsible for vagally activated antral gastrin release in dogs may not be acetylcholine. Based on studies in the rat, it has been suggested that gastrin-releasing peptide (GRP) may be this postganglionic neurotransmitter.[13]

If the net effect of acute efferent vagal stimulation is to augment gastrin release, it has been difficult to reconcile the observation that TV and even PGV, which does not denervate the antrum, increase, rather than reduce, serum gastrin levels. In these previous studies, however, the effect of vagotomy on serum gastrin in dogs was not studied acutely but instead was evaluated days, weeks, or even years after vagotomy.[4,5,7] The present study is the first to evaluate the immediate effect of truncal vagotomy on serum gastrin concentrations. Of interest serum gastrin levels decreased almost immediately after vagotomy and remained depressed for at least two hours. The acute fall in serum gastrin concentrations after vagotomy may be due to loss of cholinergic tone near postganglionic neurons that control antral gastrin release (? GRP-neurons), neurons that may possess cholinergic receptors. Such postganglionic neurons would therefore tonically release less stimulatory transmitter(s) (*e.g.*, GRP) in the vicinity of antral G cells, which would reduce tonic gastrin release from these cells into the bloodstream. At present, however, there is no method available for measuring cholinergic tone at the level of the enteric nervous system *in vivo* nor the release of GRP and other enteric neuropeptides from postganglionic canine antral neurons *in vivo*. It is uncertain for what period of time tonic antral gastrin release is



FIGS. 3A and B. Effect of truncal vagotomy (TV) or sham vagotomy (SV) on median basal gastric juice pH (A) and on mean (± SE) maximal acid outputs (MAO) (B). Preoperative studies (A, B, and C) are shown. TV or SV was performed on day 0. Significant differences are shown as *. Mean values for BAO (mmol/h) for TV or SV groups, respectively, were: study A, 3.1 ± 1.8 and 2.5 ± 0.8; study B, 2.2 ± 0.9 and 1.3 ± 0.6; study C, 2.0 ± 1.0 and 2.8 ± 1.4; postoperative day 1, 0.8 ± 0.3 and 1.5 ± 0.8; and postoperative day 7, 0.2 ± 0.1 and 0.6 ± 0.3. N = 11 for all points except postoperative study day 1 in which n = 5 for both groups.

reduced after vagal denervation because antral vagotomy *per se* does not lower fasting serum gastrin levels when measured 2 weeks or more after vagotomy.[3,4,8] Thus acute vagal denervation of the stomach lowers serum gastrin, but chronic antral denervation does not, for unclear reasons.

Studies in dogs have documented that PGV ultimately increases basal serum gastrin levels, and to approximately the same extent as does TV.[4,5,7] On the other hand, antral vagotomy does not increase basal gastrin levels in dogs.[3,4,8] Thus vagal denervation of the fundus and not the antrum is responsible for postvagotomy hypergastrinemia. Acid secretion is reduced after PGV or TV,[4,5,7] while acid secretion is unaffected by AV.[14] This suggests that reducing acid secretion could be responsible for the subsequent gastrin changes. On the other hand, Debas et al.[4] have proposed that removal of a fundic inhibitor of gastrin release is the mechanism for postvagotomy hypergastrinemia, although the nature of this inhibitor has remained elusive. Their argument is based partly on the observation that the serum gastrin response to a meal is enhanced after PGV or TV, even though the pH in the stomach after the meal is kept constant by *in vivo* intragastric titration.[4,7] However intraluminal pH and acid secretion from the time of vagotomy until the time of the meal study were not controlled in these studies. Thus it remains possible that reduced acid secretion is responsible for the ultimate hypergastrinemia that occurs after vagal denervation of the fundus.

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Key (indexing) terms: Below the abstract, provide and identify as such, three to 10 key words or short phrases that will assist indexers in cross-indexing your article and that may be published with the abstract. Use terms from the Medical Subject Headings list from *Index Medicus* whenever possible.

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The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their content, especially the Results and Discussion sections. Other types of articles such as case reports, reviews, and editorials are likely to need other formats, and authors should consult individual journals for further guidance.

Introduction: Clearly state the *purpose* of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

Hepatic Resection in the Elderly

JOSEPH G. FORTNER, M.D. and ROBERT M. LINCER, M.D.

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Between July 1, 1970 and December 31, 1988, 453 patients underwent hepatic resection by the senior author. Ninety of these patients were more than 64 years old and are the subject of this review. The 30-day operative mortality rate for all patients undergoing hepatic resection was 3.3%: major hepatic resection was 4.4% and subsegmental resection was 1.4%. The operative mortality rate for patients undergoing major hepatic resection increased incrementally with age: for patients up to age 55 years it was 0.70%, for those between 55 and 64 years it was 3.6%, and for patients older than 64 years it increased to 11.1%. This higher operative mortality rate in the elderly reflects the mortality rate for extended right hepatic lobectomy in this age group of 30.7%. If this procedure is excluded, the operative mortality rate for patients older than age 64 was 7.6%. Sixty per cent of the operative deaths were due to hepatic insufficiency. The data presented demonstrate that major hepatic resection can be performed in the elderly with a low but somewhat increased mortality risk. However, because of its markedly increased operative risk, extended right hepatic lobectomy should be performed in elderly patients only in selected cases until better methods of estimating hepatic reserve are available.

Hepatic Resection in the Elderly

The operative risk of hepatic resection for noncirrhotic livers is now generally low, with 5-year survival estimates for many hepatic neoplasms being relatively high (*i.e.*, stage I metastatic colorectal cancer 49%; stage I hepatocellular carcinoma 69%).[1,2] These advances in the 1980s have led to a need to consider candidates who might have been denied the procedure previously because of the presumed surgical risk in individuals who were older than their mid-sixties. The need is heightened by the apparent better health of older individuals today, and by a proportional increase of older individuals in the general population.

Studies on age-related mortality rates for hepatic resection are rare. The overall mortality rate is about 5%, but patient ages have either not been reported in most studies or were a mean between 49 and 62 years.[3–7] One report linked age with postoperative abdominal infections.[8] A later study found no relationship with age but attributed an increased infection rate in older individuals to certain diseases associated with aging.[9] Two reports from Japan on the risks of hepatic resections for hepatocellular carcinoma in cirrhotic livers show an increased morbidity and mortality in patients older than 65 years.[10–11]

To better evaluate the possible effects of aging on recovery from hepatic resections, 453 consecutive hepatic resections performed by the senior author (JGF) at one institution during the past 18 years were reviewed. It became apparent during the review that an increasing number of patients in the series were more than 64 years of age (Fig. 1).

Materials and Methods

The data were derived from a review of the records of the 1199 patients undergoing hepatic surgery by the senior author between 1970 and 1988. Four hundred fifty-three individuals had hepatic resections, of which 231 were for metastatic colorectal cancer, 71 for noncolonic or primary biliary tract cancer, 60 for hepatocellular carcinoma, 33 for nonhepatocellular primary liver cancer, and 58 for benign disease. Ninety of the 344 patients who had a major hepatic resection were older than 64 years and are the subject of this review. Information was collected with regard to sex, age, diagnosis, preoperative evaluation, stage of disease, operative procedure, size of lesion, perioper-

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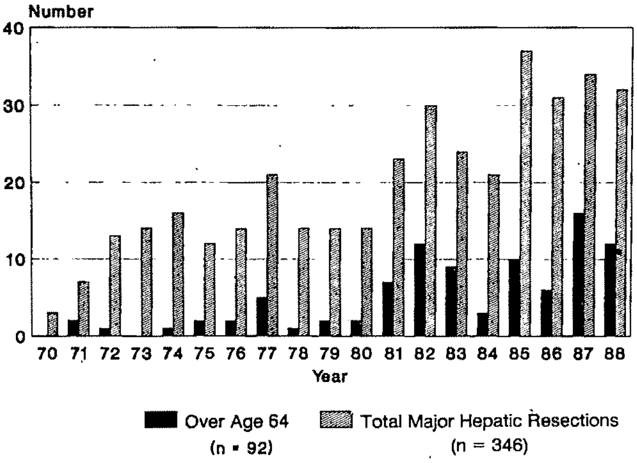

FIG. 1. Major hepatic resections in patients older than 64 years according to year of operation.

ative weight gain, operative blood loss, fluid replacement, postoperative complications, 30-day mortality rate, as well as long-term follow-up. Follow-up was complete in 93% of patients. Survival estimates were determined by the product limit (Kaplan–Meier) method. The operative technique has been previously described.[12] The data were analyzed for the group as a whole as well as for three different age groups: group I: ages 65–68 (n = 44); group II: ages 69–74 (n = 34); and group III: ages 75–82 (n = 14).

Results

The patients in the study group ranged in age from 65 to 82 years (mean, 69.9 years; median, 69 years). Fifty-eight patients were men (64.4%) and 32 were women (35.6%). There were 92 hepatic resections in 90 patients because 2 patients underwent a second resection at a later date. There were 45 right hepatic lobectomies, 11 left hepatic lobectomies, 20 lateral segmentectomies, 13 extended right lobectomies (trisegmentecomies), and 3 extended left lobe resections, with some being combined with other procedures (Table 1). Resections were performed for the following hepatic tumors: metastatic colorectal cancer (66); hepatoma (11); gallbladder cancer (4); breast cancer (2); cholangiocarcinoma (2); and once each for metastatic carcinoid, gastric carcinoma, renal cell carcinoma, embryonal sarcoma, hepatic abscess, hepatic cyst, and hemangioma.

Operative Mortality Rate

The 30-day operative mortality rate for patients undergoing hepatic resection was 3.3%: major hepatic resection was 4.4% and subsegmental resection was 1.4%. There was, however, an incremental risk with age. Patients up to 55 years of age had an operative mortality rate of 0.70% for major hepatic resection (Table 2). The rate increased to 3.6% in the group who were 55 to 64 years old. It was 11.1% in individuals older than 64 years.

Mortality rates in individuals older than 64 years varied with the magnitude of the operative procedure. Extended right hepatic lobectomy had an operative mortality rate of 30.7% (4 of 13 patients), left hepatic lobectomy had a rate of 9.1% (1 of 11 patients), right hepatic lobectomy had a rate of 8.9% (4 of 45 patients), and lateral segmentectomy had a rate of 5% (1 of 20 patients), and extended left hepatic lobectomy had a rate of 0% (none of 3 patients). The latter death was in a patient who underwent a lateral segmentectomy and subsegmental resection of the right lobe with removal of an infusaid pump as an emergency procedure for hemobilia.

The ten postoperative deaths were due predominantly to hepatic insufficiency after resection. Six patients (60%) died of this disorder, with three having undergone a tri-

TABLE 1. *Hepatic Resection Performed in Patients Older than Age 64 Between July 1, 1970 and December 31, 1988*

	Age Group (years)		
Operation	65–68 (Men/Women)	69–74 (Men/Women)	75–82 (Men/Women)
Right lobectomy only	18 (12/6)	12 (7/5)	8 (5/3)
Right lobectomy with			
Adjacent viscera	3 (0/3)	0	2 (0/2)
Left lateral segment	0	1 (1/0)	0
Subsegment	1 (1/0)	0	0
Extended right lobectomy (trisegmentectomy)	5 (4/1)	3 (2/1)	0
Extended right lobectomy with adjacent viscera	1 (1/0)	3 (1/2)	1 (0/1)
Left lobectomy	4 (4/0)	7 (7/0)	0
Extended left lobectomy	1 (1/0)	1 (1/0)	1 (0/1)
Lateral segmentectomy	9 (3/6)	6 (5/1)*	2 (0/2)
Lateral segmentectomy with subsegment right lobe	2 (2/0)†	1 (1/0)	0
Total	44 (28/16)	34 (25/9)	14 (5/9)

* Two patients had a right hepatic lobectomy initially with a lateral segmentectomy at a second operation.

† One patient had a lateral segmentectomy and resection of a subsegment with removal of an infusaid pump.

TABLE 2. *Age-Related Operative Mortality Rates for Major Hepatic Resection*

Age Group (years)	Operative Mortality Rate		
0–54	1/142 (0.70%)		
55–59	2/46 (4.3%)	4/112 = 3.6%	
60–64	2/66 (3.0%)		
65–69	6/53 (11.1%)	8/76 = 10.5%	10/90 = 11.1%
70–74	2/23 (8.6%)		
75–82	2/14 (14.3%)		

segmentectomy, two a right hepatic lobectomy, and the sixth underwent emergency lateral segmentectomy as described above. Their preoperative liver function tests were normal or minimally deviated (Table 3). Examination of nontumor portions of their resected livers revealed essentially normal findings in five patients with grossly fatty liver in the sixth. One individual died of a myocardial infarction. He had no previous cardiac history and a normal preoperative electrocardiogram. He developed a fatal myocardial infarction 12 hours after uneventful surgery. Postmortem examination revealed 90% stenosis of four cardiac vessels. Two other patients died of pneumonia and one of massive gastrointestinal bleeding.

Complications

The most common nonfatal complications were of cardiac origin. These occurred in 10 patients (12%; Table 4). Symptomatic pleural effusions developed in five patients. Transient jaundice and subphrenic abscess each occurred in four patients (4.3%), and pneumonia occurred in two.

Operative Blood Loss and Fluid Replacement

Patients who died within the 30-day postoperative period and those patients who survived were not significantly different with regard to estimated blood loss (3442 cc +/− 1919 cc *vs.* 2297 cc +/− 2123 cc), crystalloid (4305 cc +/− 2069 cc *vs.* 3005 cc +/− 1644 cc), and blood replacement (3180 cc +/− 2581 cc *vs.* 2654 cc +/− 2662 cc). Peak mean serum bilirubin levels were significantly higher in the postoperative mortality group (17.6 mg/dL +/− 16.0 mg/dL on postoperative day 9) when compared to the group that survived (4.3 mg/dL +/− 3.1 mg/dL on postoperative day 2) ($p < 0.00001$).

Length of Hospitalization

The mean postoperative hospitalization for patients older than 64 years was 15.1 +/− 9.3 days. This has lessened since 1983 to 12.8 +/− 5.2 days for elderly patients.

TABLE 3. *Postoperative Death from Hepatic Failure*

Patient Data and Procedure	Preoperative Laboratory Values HBsAg	Bilirubin 0–1.0 mg/dL	Alk Phos 1–115 U/L	SGOT 0–25 U/L	Albumin 4.0–5.2 gd	LDH 60–200 U/L
Pt. 1, 66 F Extended right Gallbladder CA	−	0.5	74	16	4.6	150
Pt. 2, 69 M Right lobe Metastatic colon CA	−	0.5	101	14	4.2	239
Pt. 3, 69 M Extended right Metastatic colon CA	+	0.4	164	25	4.6	209
Pt. 4, 67 M Extended right Metastatic colon CA	+	0.4	146	142	4.2	·24
Pt. 5, 74 M Lat. segment, right subsegment, removal infusaid pump Metastatic colon CA	−	1.0	381	53	3.2	206
Pt. 6, 67 F Right lobe Metastatic colon CA	+	0.5	76	25	4.8	163

Pt., patient; CA, ; SGOT, serum glutamic oxaloacetic transaminase; Alk Phos, alkaline phosphate; LDH, lactic dehydrogenase.

TABLE 4. *Nonfatal Complications*

Complication	Number of Patients
Cardiac	
Arrhythmias	5
Congestive failure	4
Myocardial infarction	1
Pleural effusion	5
Temporary jaundice	4
Subphrenic abscess	4
Pneumonia	2
Wound infection	2
Phlebitis	2
Pulmonary embolism	2
Intraperitoneal hemorrhage	2
Postoperative confusion	2
Biliary fistula	1
Colocutaneous fistula	1
Brachial plexus injury	1
Slow return of pulmonary function	1
Sepsis	1
Electrolyte imbalance	1
Thrombocytopenia	1
Coagulopathy	1
Prolonged ileus	1

Survival

The survival estimate for patients older than age 64 years is presented in Figure 2. The 5-year survival estimates for the various types of resection were lateral segmentectomy, 55%; extended right hepatic lobectomy, 40%; right hepatic lobectomy, 28%; and left hepatic lobectomy, 19%.

Discussion

Age proved to be a major determinant of mortality in this series of 453 hepatic resections. These procedures are safe up to age 65, with an operative mortality rate of 2.0% in 254 patients. The rate increased to 11.1% in patients 65 years of age or older, but was 7.6% if extended right hepatic lobectomy (trisegmentectomy) were avoided. These rates appear acceptable but they must be evaluated in an effort to improve the results.

Preoperative evaluation of the 90 individuals who were older than 64 years showed that only 14 patients had cardiac disease. This was treated to bring the patients into the best possible condition before operation. Only 11 patients (12.2%) developed cardiac complications after operation. Most were atrial fibrillation or supraventricular tachycardia and responded promptly to treatment. Two fatal myocardial infarctions occurred. One was fatal in a 76-year-old man who was asymptomatic and had a normal electrocardiogram before operation and an uneventful right hepatic lobectomy. The other, a nonfatal infarction, was in a patient who had a long history of cardiac disease, including a myocardial infarction, but required emergency surgery for hemobilia.

The overall incidence of infectious complications was 10% (9 of 90 patients). These included 4 subphrenic abscesses, 4 pneumonia, 2 wound infections, and 1 case of sepsis treated successfully with broad spectrum antibiotics. Most of the subphrenic abscesses occurred early in the series before closed drainage was used. This advance, when used in combination with meticulous hemostasis and prevention of bile leaks, has made subphrenic abscess a rare complication. The incidence of pneumonia in this series mandates renewed efforts to maintain pulmonary toilet, particularly in the older patients. Other infections appear to be at an irreducibly low frequency.

Fatal postoperative hepatic failure occurred in six patients, which accounts for more than one half of the postoperative deaths. Hepatic failure was manifest as hepatorenal syndrome in one individual and as progressive cholestatic icterus in five patients. This type of cholestatic icterus previously has been called posthepatectomy idiopathic cholestatic icterus.[12] Three patients with this condition underwent extended right hepatic lobectomy, one had a right hepatic lobectomy, and the fifth underwent emergency lateral segmentectomy with subsegmental resection of the right lobe and removal of an infusaid pump for hemobilia. Preoperative evaluation of the liver in these patients revealed normal or minimally elevated screening profiles (Table 3). Special liver function tests were not used. Gross examination at laporatomy revealed normal findings, except in one patient with a grossly fatty liver.

Hepatic failure in patients older than 64 years undergoing hepatic resection may be a reflection of less functional reserve and possibly a decreased ability to regenerate in the older liver. This could result in diminished capacity to tolerate the stresses of surgery, including hypovolemia, anesthesia, hypotension, or sepsis. Functionally there is pharmacokinetic evidence in elderly patients for a reduction in the metabolism of drugs metabolized by oxidation, but not those metabolized by conjugation. Separate from a decrease in hepatic blood flow there appear to be alterations in intrinsic hepatic clearance, which may result in

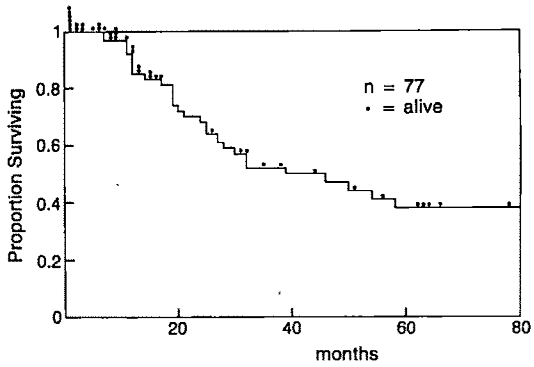

FIG. 2. Survival after major hepatic resection in patients with malignant disease who were older than 64 years.

altered first pass clearance and therefore changes in bioavailability.[13]

It is difficult to separate the cumulative effects of smoking, alcohol, and other possible adverse life style practices from those of aging alone. Associated medical illnesses, for example, infection, congestive heart failure, and diabetes mellitus may have an adverse effect. It is known that the relative weight of the liver to total body weight falls from approximately 4% in the neonate to approximately 2% in the elderly. The absolute weight of the liver also decreases throughout adult life. Blood flow also decreases with advancing age, in part, corresponding to this decrease in liver weight, but also as a result of the decrease in cardiac output with advancing age.[14]

Diminished hepatic reserve seems to be reflected in the finding that in the elderly, extended right hepatic lobectomy was the procedure with the highest operative mortality rate (30.7% [4 of 13 patients]). If extended right lobectomy had not been performed, the operative mortality rate would have been 7.6% (6 of 79 patients), which is comparable to the reported operative mortality rate of 5.8% for other major abdominal procedures in patients older than 65 years.[15] However this must be balanced against a 5-year survival estimate for extended right lobectomy of 40% (Fig. 1). Routine liver function tests have not predicted liver failure and they may be normal or show minimal deviations in spite of a decreased hepatic reserve. Better methods of estimating hepatic functional reserve, particularly in the elderly, are needed before trisegmentectomy should be done routinely in individuals who are 65 years or older.

The data presented here demonstrate that major hepatic resection can be performed with a low but somewhat increased risk of postoperative death in patients older than 64 years. This risk is commensurate with that for lesser major operative procedures. There is a markedly increased risk for trisegmentectomy and this procedure should be performed with caution until reliable methods of estimating hepatic reserve have been established. The 5-year survival estimate for patients older than 64 years undergoing hepatic resection for all types of tumors is about 40%, with an even better survival estimate for selected tumors.

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Size Reduction of the Donor Liver Is a Safe Way to Alleviate the Shortage of Size-Matched Organs in Pediatric Liver Transplantation

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The development of pediatric liver transplantation is considerably hampered by the dire shortage of small donor organs. This is a very sad situation because in most experienced centers, liver replacement can offer a long-term hope of survival of more than 70% in a growing variety of pediatric liver disorders. The reported experience with 54 reduced-size grafts on a total of 141 transplants performed in 117 children between 1984 and 1988 demonstrates that the technique of reduced-size liver transplantation not only allows long-term survival but, in fact, offers the same survival hope with the same quality of liver function, regardless of the child's age and clinical condition. The prominent feature of our experience with the reduced liver concerns its deliberate use for elective cases. Seventy-seven per cent of the 30 children who electively received a reduced liver were alive 1 year after transplantation, as were 85% of the 62 children who received a full-size graft. There is no difference in the long-term survival rate of patients who received elective grafts, which is in the range of 75% with both techniques.

THE FIRST CHILD to receive a reduced-size liver (RSL) harvested from a non–size-matched donor was operated in August 1984.[1] She was 18 months old and suffered from terminal liver failure secondary to biliary atresia. The respective weights of the donor and recipient were 35 kg and 8.5 kg. She did very well and is fully rehabilitated 4.5 years later. After this early successful experience, we became progressively confident with this technique, which we have used for 54 of the 141 grafts (39.4%) performed in 117 children who were less than 15 years old between 1984 and 1988. Initially we reserved this technique for urgent cases; recently, however, we have started to use it confidently for the elective cases and have formed our present policy of accepting any available donor for any potential candidate regardless of size unmatching (within limits defined on the basis of our growing experience). This policy allows us to keep the mortality rate of children on the waiting list relatively low at 14%.

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In this report we present a detailed account of our experience with RSL transplantation with a description of the technique, its limits, and its long-term results in a series of 117 children transplanted between 1984 and 1988. In the long term, there is no difference between the results obtained by transplanting either a full-size liver or a reduced-size graft, both in elective and urgent cases. This technique is safe and reliable and should become part of the armamentarium of every surgeon involved in pediatric liver transplantation.

Both in America and in Europe, 25% to 30% of the children on liver transplant waiting lists die before they can be treated because of the lack of size-matched donor organs.[2] The scarcity of small pediatric donors is even greater in Europe. This is a very sad situation because in most experienced centers liver replacement can offer a long-term hope of survival of more than 70% in a growing variety of pediatric liver disorders.[2–8]

From the start of our pediatric liver transplantation program in 1984, the prospect of children dying while on donor waiting lists was troublesome because two thirds of the potential recipients referred to our center are younger than 3 years of age and weigh less than 12 kilograms.[3] There is heavy ethical pressure to find a surgical alternative so that these children benefit from the larger pool of teenager and adult potential donors, the latter being offered by Eurotransplant in numbers exceeding the demand.[9]

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A videofilm describing the technique of RSL transplantation can be obtained at the cost of BF 5000. Address the order with a bank check to J.B. Otte, M.D., Department of Pediatric Surgery, University Hospital St-Luc, Avenue Hippocrate 10, B-1200 Brussels.

Description of the Procedure

Credit should be given to Bax and coworkers[10] for the first experimental study performed in the dog on the orthotopic transplantation of part of the liver and to Bismuth and Houssin[11] for the first published clinical application. Broelsch and coworkers[12] recently presented their experience with 14 children (13 urgent, 1 elective). Our own initial experience was reported in 1986[1]; several progress reports have followed,[3,13–15] including a detailed description of the technique,[16] which since has been modified on a few points. In each case the decision to perform a RSL transplantation initially is based on the donor–recipient body weight ratio and is confirmed or abrogated on the basis of visual comparison of the respective sizes of the diseased and donor livers.

Initial Preparation of the Graft

Harvesting of the donor liver is performed according to the well-standardized technique of multiorgan procurement. Preservation fluid was initially the Collins solution, although it was recently replaced by University of Wisconsin solution when this was made available to us in August 1988 for a collaborative trial within Eurotransplant. Undoubtedly the latter solution gives more flexibility due to the 2 hours of extra time needed to perform the reduction.

The work on the back table starts, as usual, with trimming of the diaphragm and dissection of the liver pedicle after proper identification of the hilar structures. Traction sutures are placed on both ends of the vena cava before its dissection away from the right liver. Constant attention should be paid to avoid untoward rewarming of the graft by keeping it immersed in the ice-cold preservation fluid during the lengthy procedure, the graft being partly elevated above the fluid only as much as needed.

Anatomical Landmarks and Extent of Reduction

The technique consists of a transparenchymal *ex vivo* right hepatectomy or lobectomy according to the Couinaud terminology (right bisegmentectomy or trisegmentectomy in the American terminology).[17] A choice is made between the two variants according to the amount of liver tissue to be removed to have a reduced liver of appropriate size to fit to the recipient liver fossa.

In both cases we detach the whole retrohepatic vena cava from the liver substance up to the outlet of the hepatic veins. This is needed for later resection of the prominent part of the caudate lobe, which reduces the sagittal diameter of the graft, and it helps to perform the portal anastomosis and the tailoring of the lower end of the vena cava when needed to approximate the size of the recipient infrahepatic vena cava (see below).

The next step is the dissection of the right hepatic vein, which is encircled close to the vena cava and then divided; the orifice in the vena cava is closed by a double running monofilament suture. The water tightness of this suture is carefully checked; additional sutures are placed when needed on the orifices of the accessory hepatic veins.

For bisegmentectomy, the resection line on the inferior surface of the liver (Fig. 1) starts just medial to the orifice of the divided right hepatic vein, runs on the right side of the IVC groove and of the caudate lobe to the right of the hilum and on the gallbladder fossa anteriorly. Over the incisure of Ganz where the posterior branch of the right Glisson's pedicle lies, transection is slightly displaced laterally to preserve the anterior branch that supplies the medial part of segment VIII (see below).

On the superior surface of the liver (Fig. 2), the line of resection is marked again from the orifice of the divided right hepatic vein to the gallbladder fossa, curving to the

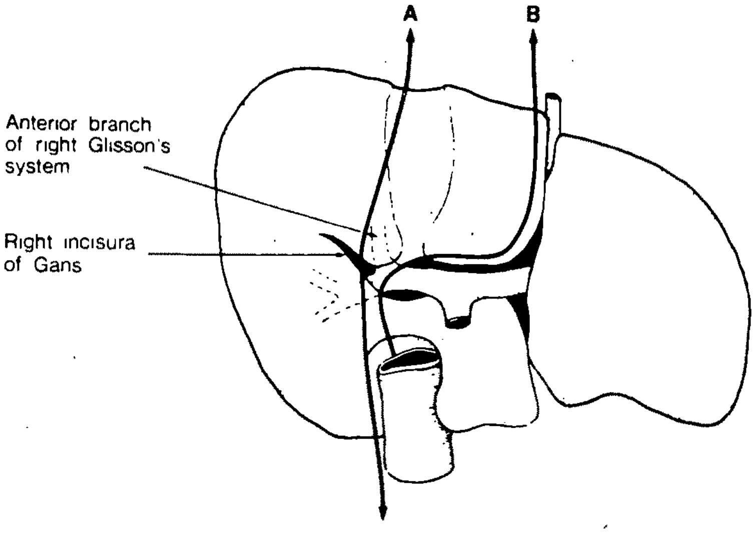

FIG. 1. Resection line on the inferior surface of the liver. (A) In case of bisegmentectomy; (B) in case of trisegmentectomy.

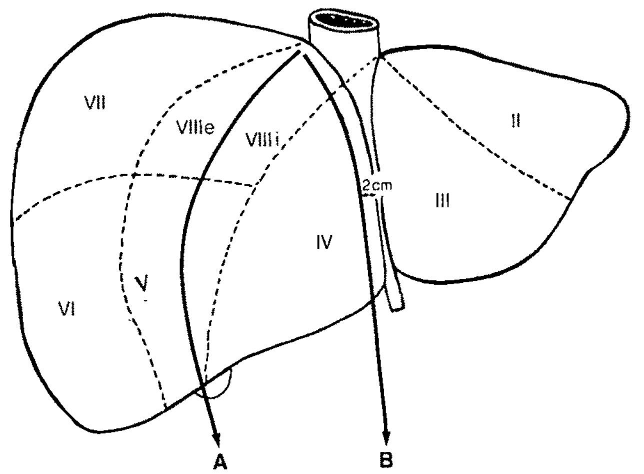

FIG. 2. Resection line on the superior surface of the liver. (A) In case of bisegmentectomy (with preservation of the internal part of segment VIII); (B) in case of trisegmentectomy. Liver segmentation according to Couinaud (see text).

right to preserve the medial part of Couinaud's segment VIII.

For trisegmentectomy the line of transection on the inferior surface follows the umbilical fissure with a margin of ± 2 cm to the right, across segment IV (quadrate lobe or medial left segment). The line of transection on the superior surface of the liver starts on the right side of the medial hepatic vein to preserve its last portion. It extends along the falciform ligament with a margin of ± 2 cm to the right to preserve the Glisson branches to segments II and III (lateral left segment)

In both technical variants the prominent part of the caudate lobe (segment I) is resected with transparenchymal division and ligation of the encountered vascular and biliary structures. The raw surface of the resected caudate lobe is then covered by approximating the edges of the liver capsule.

At the completion of the procedure, the reduced liver will comprise segments II, III, IV (left lateral and medial segments in the American terminology), and the medial part of segment VIII in the case of bisegmentectomy, and segments II and III (left lateral segment) in the case of trisegmentectomy.

Technique of Transection and Transparenchymal Division of the Glissonian Branches (Figure 3)

The liver capsule is incised with the knife over both the superior and the inferior surface as described earlier. Starting from the anterior edge, the liver is gradually divided by crushing the liver substance with a mosquito clamp. Vascular and biliary structures that resist this crushing are grasped with mosquito clamps and ligated. All glissonian branches are approached transparenchymally. The first ones to be encountered in the case of bisegmentectomy are anterior branches leading to segment V; next the posterior branches to segments VI and VII are approached through the incisura of Ganz and are divided. The last branch to be divided is the one going to the outer part of segment VIII. In the case of trisegmentectomy, the anterior and the posterior branches of the right glissonian pedicle are divided separately while the glissonian branches going to segment IV are approached while dividing the parenchyma on the right side of the falciform ligament. The medial hepatic vein is transected at some distance of its outlet in the vena cava. The major branches are closed with double running 4/0 polydioxanone (PDS) sutures.

After the liver reduction is completed, cold preservation solution is infused through the portal vein, the hepatic artery, and the common duct under appropriate pressure to check for vascular and biliary leakage. Leaks are oversewn with fine sutures of PDS. The raw surface is dried with a piece of gauze and covered with fibrin sealant (clottable protein-aprotinin-thrombin-calcium chloride solution*) that has been warmed to 37 C a few minutes before use to seal the small leaks left behind during the section of the liver substance. We apply two layers of Tissucol at 5 mL per layer.

We must stress again that throughout the entire procedure the liver must be kept immersed in the ice-cold preservation solution, except for the raw surface when it has to be exposed for sealant application.

Transplantation Technique

The reduced liver is transplanted orthotopically with slight modifications of the standard technique (Fig. 4).

The reduced graft must be rotated between 60 and 90 degrees counterclockwise around the axis of the vena cava to fill the right hepatic fossa and keep the raw surface against the posterolateral abdominal wall.

To rotate the graft on its vertical axis, the corner sutures of the suprahepatic caval anastomosis are shifted. The left corner suture is placed on the posterior margin of the vena cava at the junction between the left hepatic vein and the posterior wall. The right corner suture is placed opposite on the anterior wall. The rest of the suprahepatic caval anastomosis is done in a routine fashion, taking special care to identify the posterior wall of the donor IVC while doing the posterior suture.

The infrahepatic caval anastomosis is done next. To overcome the size discrepancy with the recipient vena cava, the donor vena cava is tailored to the appropriate size by removing a triangular portion of its anterior wall and closing the defect with a running suture; the previous

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*Tissucol, Immuno AG, Austria.

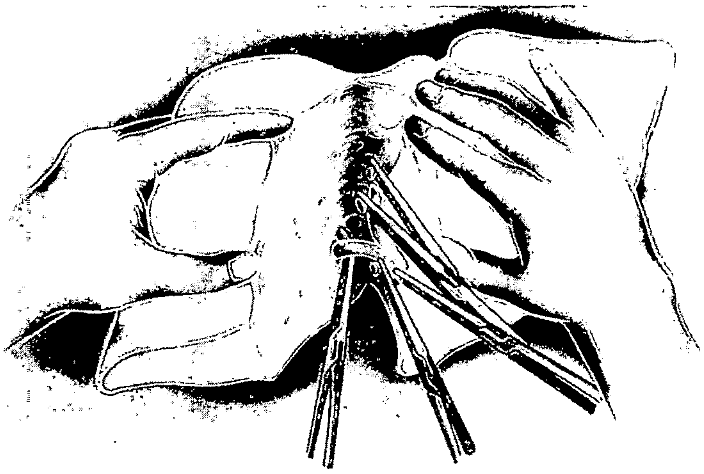

FIG. 3. Transparenchymal resection in case of bisegmentectomy: branches going to segments V and VI have been divided; pedicle of segment VII encircled by forceps; pedicle to outer part of segment VIII still intact (upper part).

full mobilization of the retrohepatic vena cava makes this tailoring much easier. The portal vein anastomosis is done in a routine fashion; size discrepancy can be overcome by resecting the recipient portal vein up to the splenomesenteric junction.

All three venous clamps are then released, allowing for portal reperfusion of the graft. Residual leaking points from the raw surface can be temporarily controlled by compression and later by extra sutures if needed.

The arterial anastomosis is performed end-to-end between the common hepatic artery or the celiac axis of the donor and the recipient proper hepatic artery at the takeoff of the gastroduodenal artery or the common hepatic artery. Alternatively, when the discrepancy is too great,

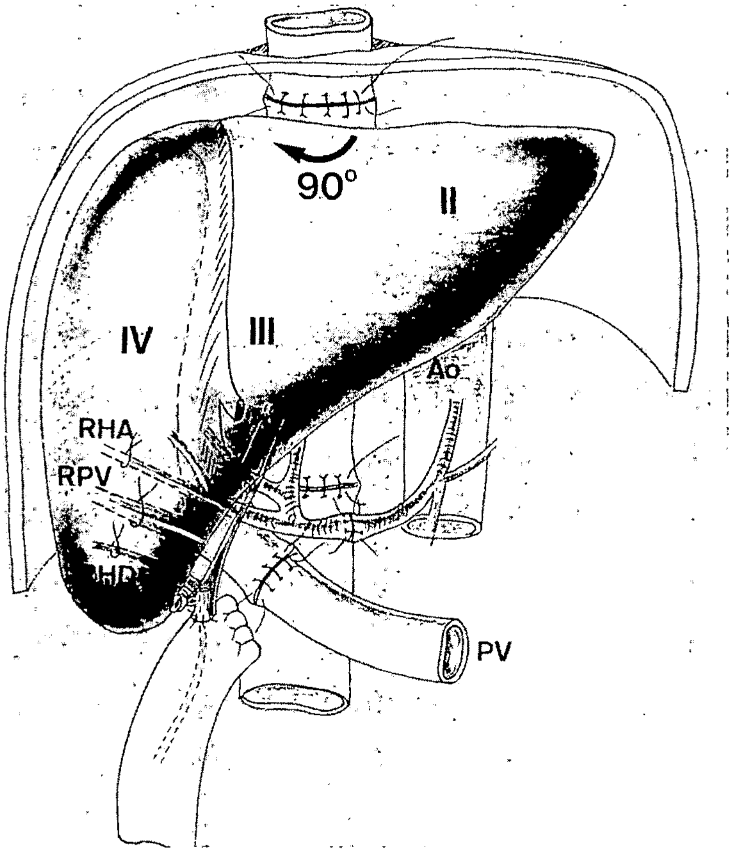

FIG. 4. Technique of orthotopic transplantation of the reduced liver (artist view). Counterclockwise rotation of the graft with transparenchymally divided pedicles of the right liver (RHA: right hepatic artery; RPV: right portal view; RHD: right hepatic duct). Most often the reduced liver comprises Couinaud segments II, III and IV (left lateral and medial segments).

the donor celiac axis is anastomosed with the recipient infrarenal aorta approached from behind the head of the pancreas, occasionally with interposition of an iliac prosthesis harvested from the same donor.[18] When it is anticipated that the portal vein will obstruct access to the artery, the arterial anastomosis can be done first.

Biliary reconstruction is always performed using a Roux-en-Y choledochojejunostomy with an internal stent brought to the skin either through the jejunal loop or the donor cystic duct. Drains are left in the peritoneal cavity, one on the left side and two on the right side, in close contact with the raw surface; the latter ones are kept under slight suction for five days to collect oozing blood.

Patients

Between March 1984 and December 1988, a total of 141 transplants were performed in 117 children. The indications for liver replacement were cholestatic diseases in 92 (biliary atresia in 86), metabolic diseases in 18, and miscellaneous in 7 (Table 1).

The age of the recipients was between 0 and 3 years in 73, (10 aged less than 1 year), between 3 and 6 years in 21, and between 6 and 14 years in 23 (Fig. 5).

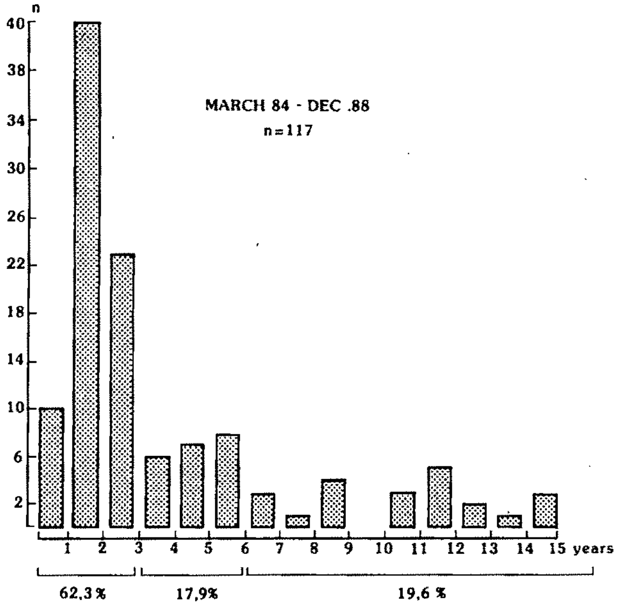

FIG. 5. Age distribution of 117 recipients.

Full-Size Liver and Technical Variants

Of the 141 grafts, 83 were full-size livers (59%) while 58 (41%) were technical variants : a reduced liver in 54, a partial or segmental graft in 1, and a split liver in 3. The only segmental graft was performed according to the technique described by the Hannover[19] and the Brisbane groups.[20]

The technique of the split liver, which we used for three children, is reported separately;[21] the fourth half liver obtained with this technique was used for an adult patient.

With the exception of two cases, the experience with the technical variants has been gained from 1986 to 1988 (Table 2). Tables 3 and 4 give the repartition for the first and the second orthotopic liver transplants (OLT) and for the age categories respectively; a similar proportion of children of every age group benefited from the technical variants. The data presented below are restricted to the reduced livers, excluding, for clarity, the four children who received either a segmental or a split liver.

TABLE 1. *Indications in 117 Children*

Indication	No. of Children (%)
Cholestatic diseases	92 (79)
Biliary atresia	86
Ductular paucity	4*
Sclerosing cholangitis	2
Metabolic diseases	18 (15)
Byler disease	6
Wilson	4
α-1-antitrypsin deficiency	2
Crigler-Najjar	2
Glycogenosis	2
Tyrosinemia	2
Miscellaneous	7 (6)
Cryptogenetic cirrhosis	3
Tumors	3
Congenital hepatic fibrosis	1*

* Two children received a combined liver and kidney transplant.

Reduced Livers

Of a total of 137 grafts performed in 113 children, 54 (39.4%) were livers reduced in size on the back table using the technique described above (Table 5).

The proportion of reduced livers was 32.6% and 62% of the elective OLT and the urgent OLT, respectively, and 37% and 50% of the first grafts and the secondary grafts, respectively.

The proportion of reduced livers was similar regarding the indications: 37.7%, 37.2%, and 33.3% of the children transplanted for cholestatic, metabolic, and miscellaneous diseases, respectively (Table 6).

Donor–Recipient Weight Ratio

The difference between the respective weights of donors and recipients can best be expressed as a weight ratio. The mean ratio was 3.5 (1.5:7.7) for the entire series of 54 reduced livers, which means that the weight of the donors exceeded the weight of the corresponding recipients by an average 250%. The mean weight ratio increased slightly over the years due to increased experience and confidence

TABLE 2. *Experience with Technical Variants According to the Years*

Year	Whole Graft	Reduced	Partial	Split Liver	Total	Recipients
1984	3	1			4	4
1985	11	1			12	11
1986	14	16			30	27
1987	32	15			47	34
1988	23	21	1	3	48	42
Total	83 (59%)	54	1	3	141	117
			41%			

with the technique (Table 7). It was lower in elective cases (3.3; range, 1.5 to 5.6) than in urgent cases (5.4; range, 4.1 to 7.7), which is explained by the greater difficulty to rapidly find a donor of appropriate size in urgent situations (Table 8). On the basis of our initial experience, we recommended not to exceed a weight ratio of 4 (300%); however we went beyond that ratio on 11 occasions, and the highest figure was 7.7 (670%) in an urgent retransplantation.

Results

Actuarial survival rates of patients and grafts were calculated according to the Kaplan–Meier method.[22] For statistical analysis, the children who were retransplanted were allocated to the group of the first graft they received (full-size or reduced graft) and survival was calculated from the time of the first transplant. The survival curves were compared by the Mantel-Haenszel test.[23]

Patient Survival

The 1-year survival rates are 77% for the entire series (N = 113), 82% and 68% of the children grafted with full-size livers (n = 71) and reduced livers (n = 42), respectively (Fig. 6). For the elective patients, the 1-year survival rates are 83%, 85%, and 77% for the entire series (N = 92), the full-size livers (n = 62), and the reduced livers (n = 30), respectively. For patients undergoing urgent procedures, the rates are 52%, 67%, and 43% for the entire series (N = 21), the full size livers (n = 9), and the reduced livers (n = 12), respectively (Fig. 7).

Graft Survival

The 1-year survival rates are 64% for the entire series (N = 137), 69% and 54% for the full size livers (n = 83) and the reduced livers (n = 54), respectively (Fig. 8). For the elective grafts, the 1-year survival rates are 75%, 79%, and 68% for the entire series (N = 93), the full-size livers (n = 63), and the reduced livers (n = 30), respectively (Fig. 9). For the urgent grafts, the rates are 38%, 40%, and 35% for the entire series (N = 44), the full-size livers (n = 20), and the reduced livers (n = 24), respectively (Fig. 10). Sixty-nine per cent of the first grafts (N = 113) were functional at 1 year (73% and 61% of the full-size livers (n = 71) and the reduced livers (n = 42), respectively). Forty per cent of the second grafts (N = 24) were functional at 1 year (50% and 29% of the full-size livers (n = 12) and the reduced livers (n = 12), respectively).

Graft Loss

Twenty-six of the 83 full-size livers were lost (31%), 17 from hepatic causes (9 instances of hepatic artery thrombosis and 6 instances of PNF) and 9 from nonhepatic causes.

Twenty-four of the 54 reduced livers were lost (44%), 12 from hepatic causes (3 instances of hepatic artery thrombosis and 3 instances of PNF) and 12 from nonhepatic causes (mostly operative deaths and infections

TABLE 3. *Experience with Technical Variants in First Grafts and Retransplantations*

	Whole Graft	Reduced	Partial	Split Liver	Total
1st OLT	71	42	1	3	117
2nd OLT	8	10			18
3rd OLT	4	1			5
4th OLT		1			1
Total	83 (59%)	54	1	3	141 (100%)
			41%		

TABLE 4. *Experience with Technical Variants According to the Age of the Children*

Age of Recipients	Whole Graft	Reduced	Partial	Split	
Less than 3 years n = 88 (62%)	55 (62%)	32	1	—	33 (38%)
3–5 years n = 26 (18%)	12 (46%)	11	—	3	14 (54%)
6–14 years n = 27 (20%)	16 (59%)	11	—	—	11 (41%)

TABLE 5. *Distribution of Grafts according to Circumstances of Transplantation*

Type of Graft	Whole Liver (%)	Reduced Liver (%)
Elective OLT n = 92	62 (67.3)	30 (32.6)
Urgent OLT n = 21	8 (38)	13 (62)
Primary graft n = 113	71 (62.8)	42 (37)
Secondary graft n = 24	12 (50)	12 (50)
Total n = 137	83 (60.6)	54 (39.4)

TABLE 7. *Donor–Recipient Weight Ratio*

	1984	1985	1986	1987	1988
Number of grafts	1	1	16	15	21
Mean ratio	4	2.3	3.25	3	4
Range	—	—	1.6–5.6	1.5–7.7	1.8–6.5
Ratio >4	—	—	2	3	6

Reduced livers, n = 54.
X = 3.5 (1.5:7.7).

observed in urgent cases and in retransplantations; Tables 9 to 11).

In addition to the 12 grafts lost due to hepatic artery thrombosis, there were six more instances of this complication in young children who remained alive without retransplantation at the cost of a biliary stricture that had to be surgically repaired. Thus the total incidence of hepatic artery thrombosis was 17% (14 of 83) for the full-size livers and 7% (4 of 54) for the reduced livers (Table 12).

Liver Function

Of 74 patients bearing functional grafts 6 months after transplantation, 67% had completely normal liver tests (serum glutamic pyruvic transaminase [SGPT], gamma-glutanyl-transferase [GGT], and bilirubin) and 14% had slightly abnormal liver tests (SGPT and gamma-GT less than twice the normal values but normal bilirubin). The corresponding figures were 63% and 20% for the full-size livers, and 76% and 4% for the reduced livers (Table 13).

Discussion

Long-term survival in the range of 70% to 80% can now be obtained in children in a growing number of liver transplant centers. Pediatric donor organs, however, are scarce, leading to deaths of a major proportion of the pediatric candidates on waiting lists before a donor of appropriate size becomes available. This shortage is particularly dire in two groups: infants and children younger than 3 years, and those needing urgent transplantations. The first category includes a large number of children referred because of unrelieved biliary atresia (representing more than two thirds of the children referred with this indication to our center[24]) or metabolic diseases leading to liver failure in early life (such as tyrosinemia and familial cholestasis).

The discrepancy between the increasing waiting list and the limited donor pool leads to an unacceptable lengthening of the waiting time which, in our center, averages 1 year for small children with blood type O and B. Meanwhile many of them suffer worsening of their condition, which leads to death on the waiting list or to anticipated transplantation in a semiurgent situation with by-passing of other children whose conditions are more elective, and attrition of the survival rates.

The second category includes the urgent liver grafting for either graft failure (due to primary nonfunction or, infrequently, at least in our experience, hepatic artery thrombosis[18] and uncontrollable acute rejection) or fulminant hepatitis; in all these circumstances, the chance of success sharply decreases when the waiting time for an appropriate donor exceeds 24 hours because of multiorgan failure and irreversible brain damage.

It is consistent with medical ethics to try new surgical techniques in desperate situations that can not be solved by standard methods if it can benefit the patient. In this context it was natural that the technique of RSL transplantation was first applied to urgent situations for which a size-matched donor could not be found; this was our experience, as well as Broelsch's,[12] because we are not as fortunate as some of our American colleagues to find easily appropriate pediatric donors for urgent grafting or re-

TABLE 6. *Reduced Livers According to Indications*

		Whole Liver				Reduced Liver			
Indications	Total	Elective	Urgent	Total	%	Elective	Urgent	Total	%
Cholestatic diseases	90	50	6	56	62.2	26	8	34	37.7
Metabolic diseases	17	8	3	11	64.7	2	4	6	35.2
Miscellaneous	6	4	—	4	66.6	2	—	2	33.3
Total	113			71					42

TABLE 8. *Donor–Recipient Weight Ratio*

	Elective (code 2)	Urgent (code 0, 1)
Number of grafts	30	24
Mean ratio	3.3	5.4
Range	1.5–5.6	4.1–7.7
Ratio >4	3	8

Reduced livers, n = 54.
X = 3.5 (1.5:7.7).

transplantation.[25] The results we have obtained in these urgent situations are in the range of 50% for long-term patient survival; the 1-year survival rate was 67% for the children transplanted in emergency situations with a full-size graft and 43% for the children who received a RSL. However up to 6 months (Fig. 6) the survival rates were very similar (67% *vs.* 64%); the increased difference between the two survival curves over 6 months was due to late deaths of children transplanted with reduced-size grafts that were unrelated to the technique (mostly infections). Moreover statistical analysis showed no significant difference between the two survival curves.

Of 13 children transplanted by Broelsch and coworkers[12] with the RSL in emergency situations, five were reported to be long-term survivors with the reduced liver, while two more had to be retransplanted with a full-size graft.

The use of a RSL for urgent transplantation seems to be validated by these data; it may be anticipated from our own experience that resorting to this technique more aggressively when a full-size graft cannot be found will improve the results. In our opinion an aggressive policy of retransplantation should include this surgical variant if the liver is not size matched.

The prominent feature of our experience with the reduced liver concerns its deliberate use for the elective cases. Seventy-seven per cent of the 30 children who received electively a reduced liver were alive 1 year after transplantation, as were 85% of the 62 children who received a full-size graft. The corresponding rates were 83% and 89% at 3 months and 83% and 87% at 6 months (Fig. 7). The increased difference between the two survival curves over 6 months was due to late deaths unrelated to the technique. Moreover statistical analysis showed no significant difference between the two survival curves. There is no statistically significant difference in the long-term survival rates of the elective grafts for either the full-size or the reduced livers.

Statistical analysis of the survival curves was also performed by allocating the retransplanted children to the group of the last graft they received (either full-size or reduced); once again no statistically significant difference was found.

We had a slightly greater graft loss for the reduced livers (44%) than for the full size grafts (31%) (Table 9), but the number of grafts lost from hepatic causes (Table 10) was similar (22% *vs.* 20%). The two cases of poorly preserved reduced livers were experienced when the Collins solution was used, which gave a too-short margin of safety in view of the two hours extra work needed by the reduction whenever there was a long-distance procurement. In this regard the UW solution undoubtedly increases the flexibility.

The relatively high incidence of operative deaths among children transplanted with a reduced liver is related to their very precarious condition at the time of transplantation or retransplantation but not to the technique.

Finally there is no difference in the long term regarding

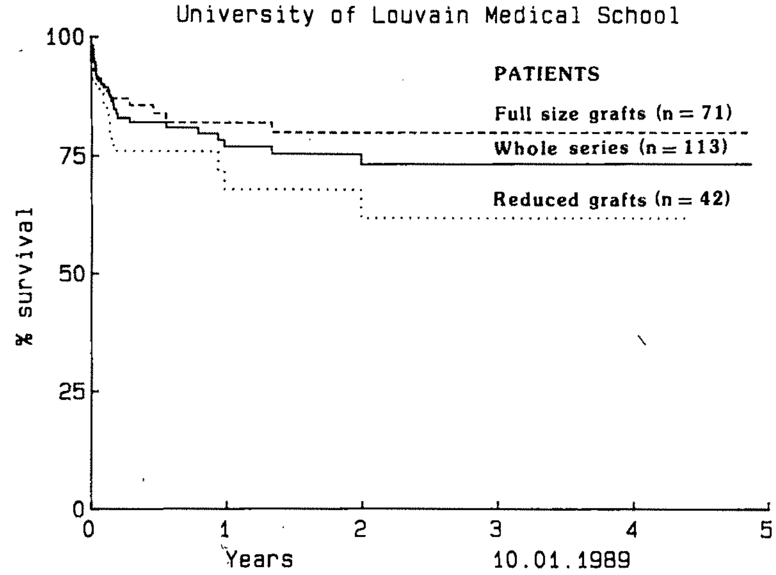

FIG. 6. Patient survival curves according to the technique used. The 1-year survival rate is 77% for the whole series, 82%, and 68% for the children grafted with full-size livers, and the reduced-size livers, respectively.

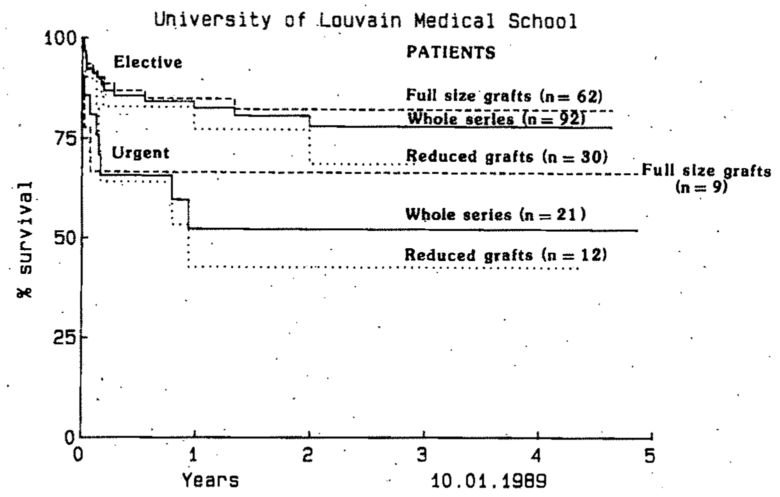

FIG. 7. Patient survival curves according to the circumstances of the transplant. For the elective patients, the 1-year survival rates are 83%, 85%, and 77% for the whole series, the full-size livers, and the reduced-size livers, respectively. For the urgent patients, the respective rates are 52%, 67%, and 43%.

the quality of the liver function (Table 13). Of the 49 children bearing a functional full-size graft 6 months after transplantation, 63% and 20% had completely normal or slightly abnormal liver tests, respectively; the corresponding rates for the 25 children bearing a reduced liver are 76% and 4%. These data show clearly that full rehabilitation is provided equally by the transplantation of a reduced-size liver.

Proceeding by errors and trials, we refined the method. Now we would like to offer the following comments regarding the technique and the possible extent of its application.

When a donor liver has to be reduced in size, it seems logical to discard the bigger part and preserve the smaller one. For this reason we have always used the left lobe, thus preserving the maximal amount of liver tissue that could fit into the liver fossa while allowing an easy closure of the abdominal wall. Depending on the visual comparison of the size and the shape of the two livers, we decide, case by case, how much to resect; the largest reduced liver includes the anatomical left lobe (Couinaud's segments II, III, and IV) and the medial part of segment VIII (this latter detail also gives the raw surface a curved shape, fitting best to the posterior wall of the right liver fossa), while the smallest reduced liver includes only the lateral segment of the left lobe (Couinaud's segments II and III). In between, depending on the available space, we may resect also the medial part of segment VIII and even some part of segment IV (left medial segment), giving the technique maximal flexibility. Proceeding that way and rotating the graft counterclockwise, we never had any serious problem with abdominal closure.

In our first cases we followed the description given by Bismuth and Houssin,[11] placing the reduced liver in its anatomical position in the midepigastric area. The resulting drawbacks were a dead space in the right hypochondrium, which was prone to accumulate blood oozing from the raw surface and the operative field, occasional

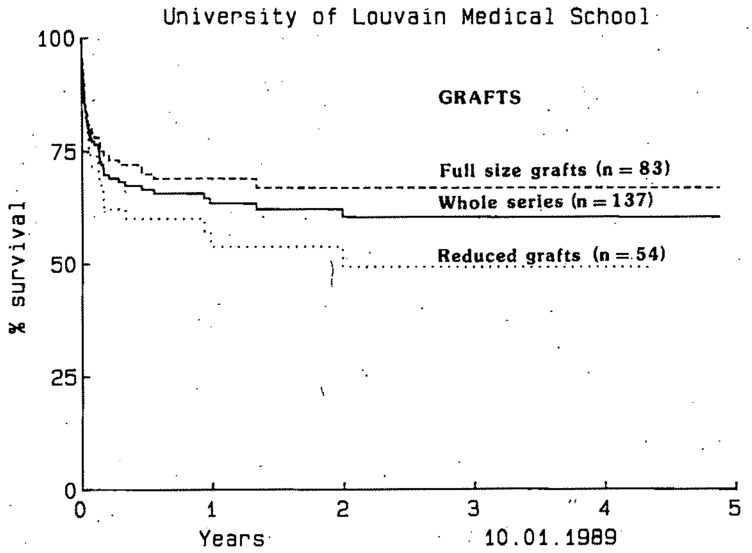

FIG. 8. Graft survival curves according to the technique used. The 1-year survival rates are 64%, 69%, and 54% for the entire series, the full-size grafts, and the reduced-size grafts, respectively.

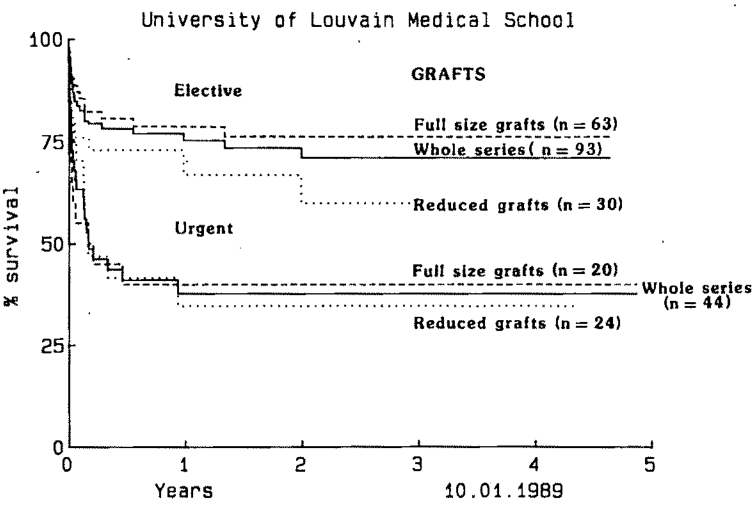

FIG. 9. Graft survival curves according to the circumstances of the transplant. For the elective grafts, 1-year survival rates are 75%, 79%, and 68% for the whole series, the full-size grafts, and the reduced-size grafts, respectively. For the urgent grafts, the respective rates are 38%, 40%, and 35%.

difficulties in the closure of the abdomen due to the bulky shape and size of the reduced graft, and possible twisting of the vascular inflow and outflow caused by the displacement of the graft to the empty right liver fossa occurring during the closure under tension of the abdominal wall.

All these drawbacks can be easily prevented by rotating the graft counterclockwise to the right by 60 to 90 degrees around the axis of the vena cava. As described earlier, this rotation is simply obtained by shifting the corner sutures of the suprahepatic caval anastomosis Since we have adopted these details, which have soon become a routine part of our current technique, the incidence of blood collection close to the raw surface, which is sometimes secondarily infected, has been eliminated.

Hepatic artery thrombosis is a well-known complication of pediatric liver transplantation, with reported incidence varying between 6%[2] and 40%.[18,26–28] Our own incidence in the present series of 137 grafts was 13%. There was a much lower incidence in children who received a RSL (7%) than a full-size graft (17%). The explanation for this impressive difference is not univocal. Undoubtedly the size of the vascular supply plays a role, as suggested by the higher incidence of thrombosis in children younger than 1 year who receive a size-matched liver, which was observed both in Pittsburgh[29] and in our center.[18] The bigger size of the arterial supply of the reduced liver offers some protection, but also, we believe, the lesser increase in the abdominal pressure resulting from the closure of the wall. Houssin,[30] using implantable doppler probes, has proved that closure of the abdomen resulted in a significant drop of the arterial flow, even after transplantation of a size-matched liver. Due to the shortage of small pediatric donors, we have often transplanted full-size livers, despite the fact that the difference between the donor and recipient weights was more than 20%, which is considered by Shaw and coworkers to be the safe limit.[2] Another complication that might result from this situation is a pressure necrosis of the right lobe, as we have experienced in two children who required a secondary right lobectomy.

During the most recent part of our experience, we have

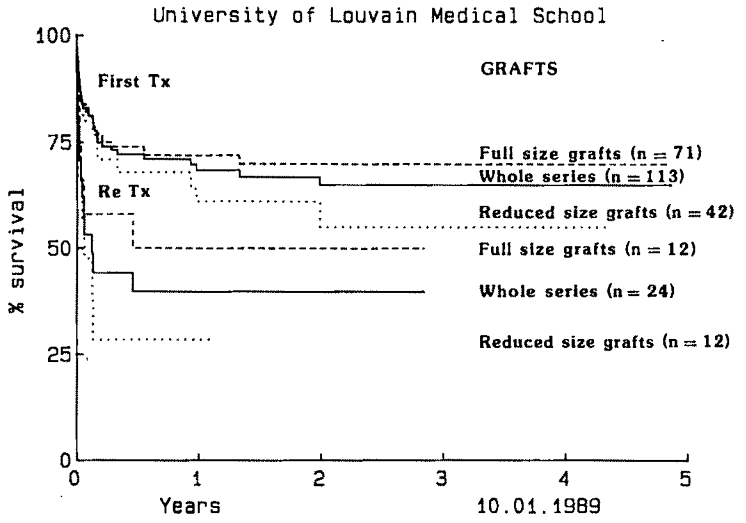

FIG. 10. Graft survival curves of the first grafts and retransplants (re Tx). In the first category, the 1-year survival rates are 69%, 73%, and 61% for the whole series, the full-size grafts, and the reduced-size grafts, respectively. The corresponding figures for the retransplants are 44%, 50%, and 29%.

TABLE 9. *Graft Loss*

Causes of Graft Loss	Full-Size Livers 26/83 (31%)	Reduced Livers 24/54 (44%)
Hepatic	17 (20%)	12 (22%)
Nonhepatic	9 (11%)	12 (22%)

reduced the graft size more and more liberally; this policy, combined with technical refinements including routine use of magnification with 5.5 × loupes and early use within the first 24 hours of antiaggregant substances (Dipyramidol 7 mg/kg and aspirin 3 mg/kg per day), led to a drastic decrease of the arterial thrombosis rate: among 44 transplants performed in 1988 in 35 children with either a full-size graft or a reduced liver, only 4 (9%) were complicated by arterial thrombosis (2 of 23 full-size grafts and 2 of 21 reduced grafts).

To identify the vascular and the biliary structures to be divided, we prefer the transparenchymal approach, but the hilar approach used by Broelsch[12] is undoubtedly of equivalent value; both are commonly used in resection for hepatic masses. The transparenchymal approach is safer, allows more flexibility in tailoring the liver mass to a size fit for use in each individual case, and protects the vascular supply of the common bile duct originating from the right hepatic artery. We have never observed any ischemic necrosis of the common bile duct of a reduced liver with a patent hepatic artery.

Some guidelines are needed regarding the acceptable difference between the potential donor and recipient weights before embarking on a RSL transplantation. We reported earlier that a weight ratio of 4 was the safe limit not to be exceeded.[3] However with increasing experience we have recently exceeded this ratio in 11 occasions, both in urgent retransplantations for graft failure and in elective cases. Such was the case in 2 of 16 reduced livers grafted in 1986, 3 of 15 in 1987, and 6 of 21 in 1988 (Table 7). The highest weight ratio was 7.7 and we would agree with Broelsch[12] that surgeons having extended experience with the technique can go up to a weight ratio of 6, although we would recommend that less experienced surgeons not exceed a weight ratio of 3 or 4.

Some authors such as Busutill[25] and Burdelski[31] have argued that the technique might potentially reduce the pool of grafts that might be more appropriately suited for those older pediatric recipients who would have a more favorable prognosis; we believe that this is specious and conservative reasoning. First the pool of donors in the adolescent age group is larger than that of infants and small children, whereas the need for liver replacement is the highest in young children because of the age distribution of pediatric liver diseases; moreover in Eurotransplant[9] the pool of adult donors exceeds the demand. Second the technique can be used in any age group; we have used it for 38% of the children younger than 3 years, 54% of the children between 3 and 6 years, and in 41% of the children between 6 and 14 years (Table 4). We also used it in adult patients of small size. Taking into account the age distribution of both the donor and recipient pools and the reliable safety of the RSL technique as demonstrated by the present report, we believe that this technique allows a more even access to and a more fair distribution of the donor organs. The technical barriers having been taken down, it is logical and ethically justified to systematically organize a shift of the donor organs down the age scale.

TABLE 10. *Hepatic Causes of Graft Loss*

Causes of Graft Loss	Full-Size Livers	Reduced Livers
HA thrombosis	9	3
Low portal flow	—	1
PNF	6	3
Poor preservation	—	2
Nonvascular necrosis	1	—
Rejection	—	2
Hepatitis	—	1
Tumor recurrence	1	—

TABLE 11. *Nonhepatic Causes of Graft Loss*

Causes of Graft Loss	Full-Size Livers	Reduced Livers
Operative death	1	4
Heart failure (glyc. stor. dis. IV)	—	1
Iatrogenic	2	—
Infection	6	6
CVA	—	1

Mastering the technique of RSL transplantation has already led to new technical developments such as the segmental graft and opens new avenues of experimental and clinical research. The segmental graft technique (partial liver) differs from the reduced liver in one main point: the retrohepatic vena cava of the recipient is preserved during hepatectomy and a direct anastomosis between the donor left hepatic vein and the vena cava orifice of the recipient hepatic veins is performed.[19,20] This technical modification allows transplantation into small children of segments of adult livers up to a weight ratio of 8 to 9.

Future avenues of research include segmental grafts removed from adult related living donors; experimental work in progress in several laboratories, including our own, and extended clinical experience with liver resection as well as with the technical variants of liver transplantation, of which the reduced liver is only one, will likely allow future clinical application. However ethical problems remain to be solved. A first case, although unsuc-

TABLE 12. *Hepatic Artery Thrombosis*

Type of Graft	Number with Thrombosis
Full-size livers	14/83 (17%)
Reduced-size livers	4/54 (7%)
Total	18/137 (13%)

TABLE 13. *Liver Tests—6 Months After Transplantation*

Liver Tests	Normal	Slightly Abnormal	Severely Abnormal
SGPT (Iu/L)	<32	32–60	>60
GT (Iu/L)	<45	45–90	>90
Bilirubin (mg%)	<1	<1	>1
Full-size livers (n = 49)	31	10	8
Reduced livers (n = 25)	19	1	5

SGPT, serum glutamic pyruvic transaminase.
GGT, gamma-glutamyl-transferase.

cessful, was already tried in Brazil. Another very attractive field is represented by some metabolic diseases not affecting the liver, such as Crigler-Najjar syndrome, oxalosis, and hemophilia in which an *in situ* auxiliary left segmental graft replacing the removed native left lobe of the recipient would be a more clever and less disturbing (for the surgeon) procedure than the total removal of a perfectly functioning liver but for a single enzyme.

Another procedure worthy of careful exploration by surgeons experienced with the reduced liver technique is the split liver. In this technique the liver parenchyma of the donor liver is divided into two parts with partition of the liver pedicle to obtain two viable grafts fit for use. We have recently transplanted three children and one adult with the grafts obtained from two such split livers with two successes.[21] Other cases have been performed in Hannover, Paris, and Chicago by surgeons extensively experienced with the reduced liver technique.

The experience reported here, which is now the largest worldwide, demonstrates that the technique of RSL transplantation not only allows long-term survival but, in fact, offers the same survival hope with the same quality of liver function, whatever the age and clinical condition of the child. The technique is safe and reliable and we recommend it as the definitive treatment in urgent and elective cases. It allows a more flexible use of the donor organ resources and is a valuable way to overcome the shortage of pediatric liver donors. This technological improvement will undoubtedly booster the development of pediatric liver transplantation if these children are allowed to benefit from the larger pool of teenager and adult donor livers, as is done in several European liver transplant centers.

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Successful Segmental Intestinal Transplantation in Enterectomized Pigs

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The aim of this study was to determine whether short-segment jejunal allografts maintained the viability and nutritional status of outbred recipient pigs treated with low-dose cyclosporine. The animals were subjected to total small bowel resection (from the ligament of Treitz to the ileocecal valve, approximately 15 m). Short-gut control animals (n = 8) who had no transplant died of malabsorption on day 62.5 ± 4.1 (mean ± SEM). Without cyclosporine immunosuppression, recipients (n = 5) of 3 m to 4 m jejunal allografts died of rejection on day 8.8 ± 0.7. However enterectomized pigs (n = 11) who had segmental jejunal allograft transplants and were treated with cyclosporine (10 mg/kg/day) demonstrated significantly prolonged survival (to day 80.9 ± 22.3; $p < 0.05$). By 180 days after transplant, surviving animals increased their weight by almost 40%. In conclusion short-segment jejunal allografts significantly improved the mortality and morbidity rates from surgically created short bowel syndrome in pigs.

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REJECTION AND GRAFT-VERSUS-HOST disease (GVHD) are both potential obstacles to successful allotransplantation of small intestine.[1] It has been assumed that high-dose immunosuppression would be required to overcome detrimental immunologic responses. Large doses of cyclosporine have, in fact, been used even in rat models.[2,3] However in clinical transplantation allograft recipients should be maintained on the lowest possible doses of immunosuppressive agents to avoid lethal infection and the development of lymphoproliferative disorders as well as to minimize organ toxicity. Acceptably low dose regimens of immunosuppressive agents recently have been sought for use in intestinal transplantation. We have previously demonstrated that reduced daily doses of cyclosporine are sufficient to prevent rejection of intestinal allografts when short segments are transplanted.[4] Even in the absence of cyclosporine, segmental jejunal grafts caused no deaths in a unidirectional GVHD model, while total small bowel or ileal grafts resulted in a 100% mortality rate by day 21.[5] Murine recipients of short-segment intestinal allografts have been maintained successfully on a low-dose (5 mg/kg/day) short-term (28 days) cyclosporine regimen for more than 150 days after transplantation, even across major histocompatibility barriers.[6] A major disadvantage of short-segment orthotopic intestinal grafts in the treatment of the short-gut syndrome was assumed to be the limited absorptive surface area. However, despite this limitation of surface area, segmental intestinal grafts have been shown to maintain steady growth of enterectomized animals and to undergo considerable morphologic hypertrophic change.[7] The immunologic advantages and the absorptive compensatory ability of segmental intestinal grafts mandate a trial of this allograft technique supplemented by a low-dose cyclosporine regimen in outbred large animals. Should segmental intestinal allografts support progressive growth of large animals with surgically created short-gut syndrome, this approach would provide a solution for the limited availability of donor graft tissue for clinical transplantation. Using this approach living relatives could potentially donate allogeneically similar segments of intestine to serve as grafts for family members with severe short-gut syndrome.

The aim of this study was to determine whether segmental intestinal allografts in conjunction with a low-dose cyclosporine regimen maintain the viability and nutrition of outbred pigs with surgically created short bowel syndrome.

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Materials and Methods

Animals

Outbred female pigs (no littermates) weighing 15 to 40 kg were used (Earle Parsons and Sons, Hadley, MA). They were divided into three groups: group 1, short-gut controls (n = 8); group 2, transplantation without cyclosporine (n = 5); and group 3, transplantation with a low-dose cyclosporine regimen (n = 11). Animals were fasted for 18 hours before the operation but were allowed free access to water.

Anesthesia

Ketamine (22 mg/kg) and acetylpromazine (1.1 mg/kg) were injected intramuscularly as premedication. Anesthesia was maintained using 2.5% thiopental sodium administered by intravenous drip infusion (*via* an ear vein) supplemented with intramuscular ketamine injections (10 mg/kg) at approximately 1-hour intervals. Endotracheal intubation was not performed. During the operations, animals breathed spontaneously. Atropine sulfate (0.02 mg/kg) and Combiotic® (2 mL) were injected intramuscularly just before laparotomy.

Short-Gut Controls

Following a midline incision, the entire small bowel (approximately 15 m) was removed from the ligament of Treitz to the terminal ileum (less than 2 cm proximal to the ileocecal valve). Intestinal continuity was restored in each animal by end-to-end anastomosis (two-layer, hand-sewn with 4-0 silk) between the distal duodenum and the very terminal ileum. Once the mesenteric defects were closed, the abdomen was closed.

Short-Segment Intestinal Transplantation

Two animals were prepared for transplantation of small intestine to each other. Each animal thus served as both graft donor and recipient. A graft from animal A was transplanted into animal B and vice versa.

Graft preparation. Following a midline incision, 3 m to 4 m jejunal segments (measured to approximate 25% of the length of the entire small bowel) were isolated. Animals were systemically heparinized (100 U/kg). Each segmental graft had a vascular pedicle that consisted of one jejunal artery and one vein. After harvesting the segment and clamping the proximal vessels for reanastomosis, the remaining small bowel from the ligament of Treitz to the ileocecal valve (approximately 11 m to 12 m) was resected and discarded. The isolated jejunal grafts were kept in a cold (4 C) normal saline bath and each vascular bed was perfused by gravity flow *via* the artery with 250 cc of cold normal saline solution containing 2500 units of heparin sodium until the venous effluent was cleared of blood.

Recipient operation. The segmental jejunal grafts were placed orthotopically. Revascularization was performed between the donor jejunal artery and a branch of the recipient superior mesenteric artery. This was accomplished in either end-to-end or end-to-side fashion with 7-0 monofilament nylon continuous sutures. Using 7-0 Tevdek®, venous anastamosis was performed. Functional isoperistaltic bowel continuity was restored between recipient and graft by duodenojejunostomy and jejunoileostomy, both in end-to-end fashion. The mesenteric defects were closed and the mesentery of each graft was carefully fixed to avoid tension or kinking at the sites of vascular anastomosis. The abdomens were then closed. Approximately 1000 cc of normal saline was infused intravenously during the course of each surgical procedure.

Postoperative care. The animals were returned to their pens on waking. On the first postoperative day they were not permitted food or water. On postoperative day 1, only water was provided. Food and water were allowed ad lib beginning on postoperative day 2 and thereafter. No antibiotics or intravenous fluids were required after operation.

Animal care. The study was approved by the Animal Care and Use Committee of the State University of New York, Health Science Center at Brooklyn. Animal studies were conducted in accordance with National Institutes of Health guidelines for the care of experimental animals. To avoid unnecessary pain or discomfort of the experimental animals, the animals were killed when any of the following criteria were met: (1) loss of more than 35% of preoperative body weight; (2) discoloration of the nose or ears; (3) nausea and vomiting; (4) diminished food intake; or (5) lethargy or diminished activity.

Animals that died within 5 days after operation were considered technical failures and were excluded from the study. Autopsy was performed on all animals.

Immunosuppressive regimen. Cyclsoporin A was supplied by Sandoz, Inc., East Hanover, NJ. In group 3 (transplantation with a low-dose cyclosporine regimen), cyclosporine (CsA), 10 mg/kg, was injected intramuscularly daily from day 0 to day 100. From day 101, CsA was administered on alternate days. Vitamin B_{12} (1μ g/kg) was supplemented twice monthly to avoid vitamin deficiency anemia.

Survival time, changes in body weight, and routine laboratory blood chemistry data were recorded. Tissue specimens were harvested at the time of animal death and studied histologically.

Statistics. All data were expressed as mean ± SEM. The Wilcoxon signed-rank test was used for analysis of survival. For other parameters the Student's t test and analysis of variance were used. P values of less than 0.05 were considered significant.

Results

Short-Gut Controls

Eight pigs whose entire small intestines were resected developed persistent diarrhea and progressively lost weight, despite adequate intake of food and water. Eventually all animals were killed because of severe weight loss (more than 35% of preoperative body weight) between days 54 and 90 (mean survival, 62.5 ± 4.1 days). At autopsy no abscesses, obstruction, or bowel leaks were noted.

Transplantation

Of the total 20 transplants, 4 (20%) died of technical failures (vascular thrombosis) within the first 5 days after operation and were thus excluded from this study.

Enterectomized animals (n = 5) who had segmental jejunal allografts, but received no cyclosporine, died of rejection on day 8.8 ± 0.7 (mean ± SEM). At autopsy it was apparent that the transplanted bowel had deteriorated into a hard, whitish, irregular mass. The mesenteric lymph nodes were quite enlarged. Histologically there was clear-cut evidence of rejection with loss of villus mucosal integrity and infiltration of the submucosa with chronic inflammatory cells.

The 11 treated transplant recipients tolerated the cyclosporine without complications. Intramuscular CsA administration (10 mg/kg), in age- and body weight-matched control pigs (n = 8), resulted in mean blood levels of cyclosporine of 522 ± 240 ng/mL at 1 hour, 139 ± 39 ng/mL at 4 hours, and 81 ± 28 at 24 hours. At 100 days after operation, the mean CsA trough level was 372 ± 158 ng/mL.

Recipients of segmental jejunal allografts treated with 10 mg/kg CsA daily (n = 11) survived for an average of 80.9 ± 22.3 days ($p < 0.05$ compared to the short gut control and nonimmunosuppressed transplant groups; Table 1). These animals gained body weight and thrived (Fig. 1). They maintained normal serum proteins (Table 2). Of 11 animals 5 (45%) survived more than 3 months and 3 (27%) thrived for more than 6 months before they were killed for histologic study of the bowel. Eight pigs died between days 12 and 136 after operation. Causes of death at autopsy, listed in Table 3, included venous obstruction (day 12), abdominal abscess (day 16), ileus (day 25), and rejection (day 91). However four animals had no obvious identifiable cause of death; there was no evidence of rejection or infection at autopsy.

None of the animals that survived for more than 180 days had any evidence of abscess formation, hepatosplenomegaly, or cholelithiasis. In all three pigs the transplanted intestine had a normal appearance at autopsy with no evidence of swelling of the gut or the mesenteric lymph nodes. Histologically the bowel retained its mucosal integrity and there was no significant lymphocyte infiltration (Fig. 2).

Discussion

Although 30 years have elapsed since the development of experimental small intestinal transplantation by Lillehei and colleagues,[8] there has been little, if any, substantiation that orthotopic bowel transplants improve the morbidity and mortality rates of enterectomized large animals. Thus there has not been any experimental justification for the application of this therapy to human short-gut syndrome. Most of the previous studies of small intestinal transplantation[9–14] have been designed to examine the efficacy of various immunosuppressive regimens in improving the survival of untreated transplanted animals, rather than defining the benefit of transplantation of functioning bowel into animals with short-gut syndrome. In fact, only one previous study included a no-transplant short-gut group.[11] In contrast the present study has clearly demonstrated that segmental jejunal allotransplantation is an effective means of treating enterectomized outbred pigs. Immunosuppressive therapy with low-dose cyclosporine provided for growth and improved survival of the recipients as compared to untreated short-gut control animals. While our 27% (3 of 11) long-term success rate is far from ideal, it is certainly optimistic.

TABLE 1. *Survival After Total Small Bowel Resection*

Group	Procedure	Days (Mean ± SEM)
Group I	Short-gut control (n = 8)	54, 57, 57, 57, 57, 64, 64, 90 (62.5 ± 4.1)
Group II	Transplantation without CsA (n = 5)	7, 8, 9, 9, 11 (8.8 ± 0.7)
Group III	With CsA (n = 11)	12, 16, 17, 18, 25, 35, 91, 136, >180, >180, >180* (>80.9 ± 22.3)*

* $p < 0.05$ compared to both groups I and II groups by Wilcoxon signed-rank test.

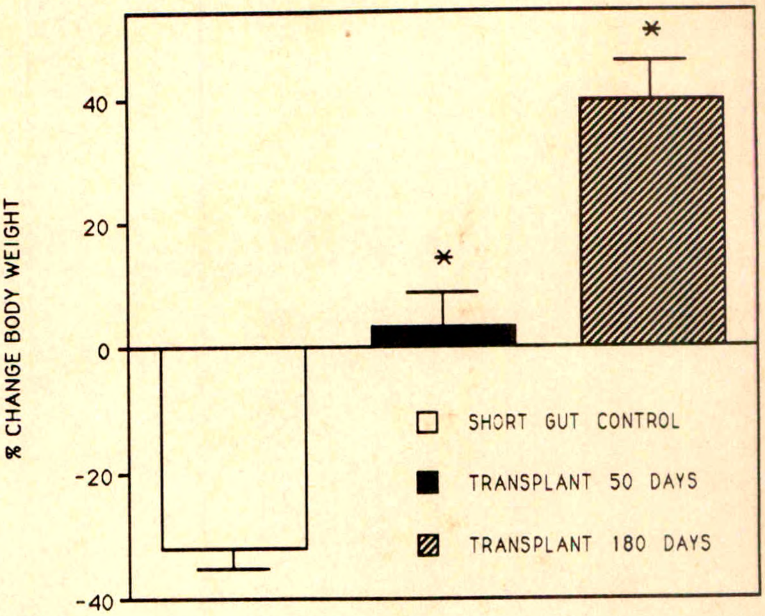

FIG. 1. By postoperative day 50, totally enterectomized control animals lost 32% ± 3.5% of their preoperative body weights. CsA-treated recipients of segmental jejunal allografts regained their preoperative weights by day 50 and had a 39.3 ± 6.4% increase in body weight 180 days after transplantation.

We have previously reported that short-segment intestinal grafts improved the survival of enterectomized rats treated with low-dose cyclosporine.[6,7] The present results obtained using outbred pigs have served to confirm our earlier findings. Therefore our experimental experience documents that segmental jejunal allotransplantation in association with only a low-dose cyclosporine immunosuppressive regimen is efficacious. The benefits of using segmental intestinal grafts as compared to transplanting the entire small bowel has become evident on reviewing the immunologic responses, the absorptive function, and the technical requirements of the transplanted small bowel.

Although Lillehei et al.[15] implicated GVHD as a major cause of death after intestinal transplantation, this phenomenon has been difficult to document in large animals. The immunologic predominance of rejection has been postulated to mask the signs of GVHD.[1] In addition it is likely that the recipients' rejection reaction against the allografted bowel would be capable of eliminating the carrier donor lymphocytes responsible for initiating GVHD. Nonetheless the immunologically well-defined models of small intestinal transplantation in rats first described by Monchik and Russell[16] clearly defined both the existence and the fatal consequences of rejection and GVHD. In our previous studies using a unidirectional GVHD model of total small bowel transplantation, all the animals died by day 21; however no deaths were observed after transplantation of short segments of jejunum, even without the use of immunosuppressive agents.[5] These results in the rat are consistent with the observation that large-animal recipients of entire bowel grafts suffer from GVHD, whereas recipients of segmental intestinal allografts develop rejection but not GVHD.[17] In our study there were no documented deaths from GVHD in any of the 16 allograft recipients, regardless of the immunosuppressive therapy used. These results, in addition to those described in the previously cited studies, support the hypothesis that reduction of the amount of lymphoid tissue in intestinal grafts lessens the severity of GVHD.

Rejection is the major immunologic impediment to successful small intestinal allotransplantation. In rats we have previously demonstrated that short intestinal graft segments exhibited immunologic advantages in that they required lower daily doses of cyclosporine to suppress re-

TABLE 2. *Blood Chemistries on Postoperative Day 50*

Laboratory Data	Transplant with CsA	Short-Gut Control	Normal Control
Hemoglobin (g/dL)	9.9 ± 0.5	9.8 ± 0.6	9.7 ± 0.3
Hematocrit (%)	29.6 ± 1.3	30.3 ± 1.2	30.0 ± 0.8
Serum Sodium (mEq/L)	124 ± 2.7	129 ± 4.4	122 ± 2.0
Serum Potassium (mEq/L)	5.3 ± 0.2	4.1 ± 0.3	5.2 ± 0.2
Serum Chloride (mEq/L)	93 ± 0.8	92 ± 2.7	100 ± 1.2
Total Protein (g/dL)	6.4 ± 0.4	5.8 ± 0.5	6.0 ± 0.3
Serum Creatinine (mg/dL)	1.47 ± 0.05	1.2 ± 0.11	1.14 ± 0.06

TABLE 3. *Causes of Death*

Short-Gut Control	Transplantation Without CsA	Transplantation with CsA
8/8 Malabsorption	5/5 Rejection	1/11 Venous Obstruction 1/11 Abscess 1/11 Ileus 1/11 Rejection 4/11 Unknown 3/11 Survivors >180 days

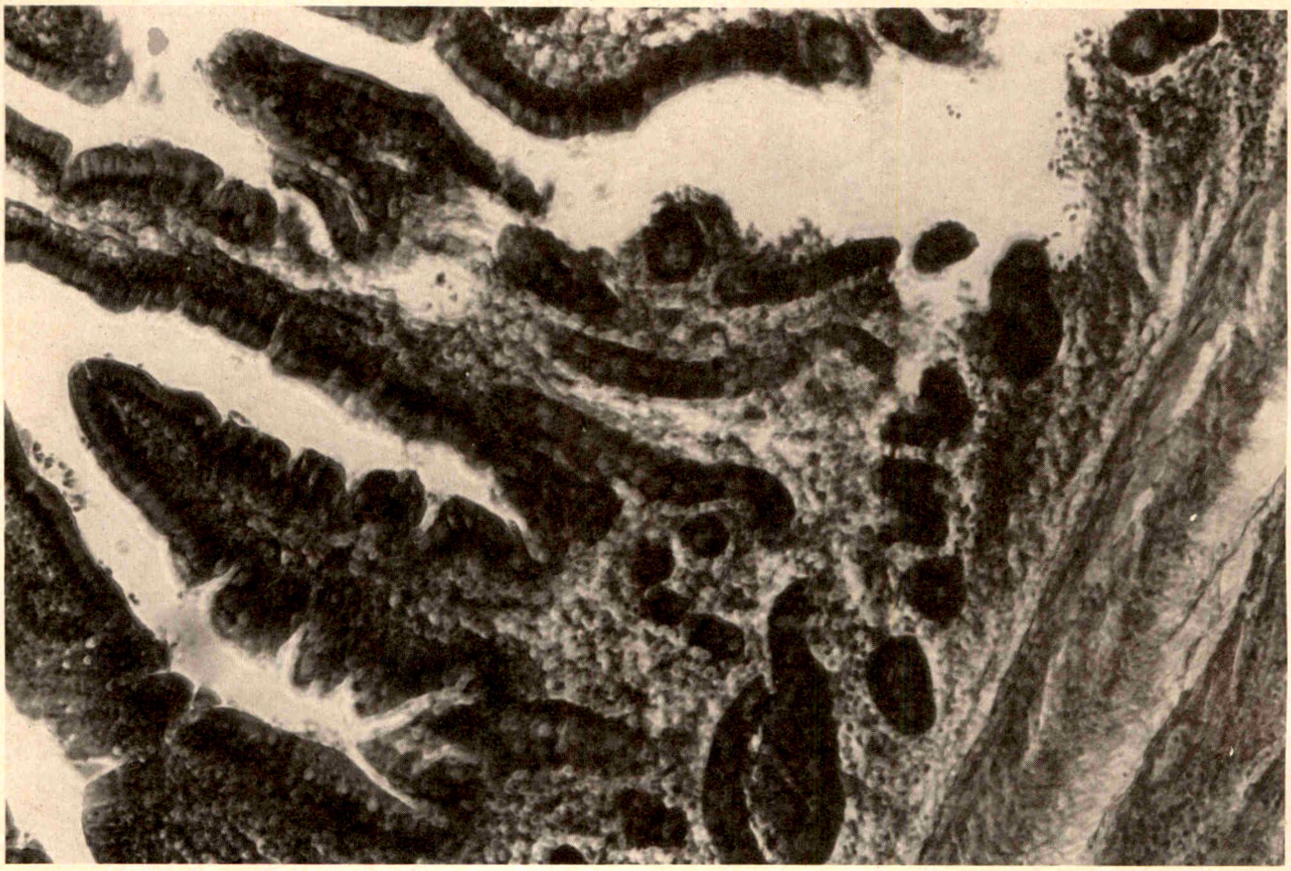

FIG. 2. Histologic section of a jejunal allograft 6 months after transplantation. Mucosal integrity is well preserved and there are no signs of rejection.

jection.[4] A dose of 5 mg/kg/day administered intramuscularly was sufficient to protect animals against intestinal allograft rejection, even those traversing major histocompatibility barriers. Successful use of this low-dose regimen has been supported by the study of Shimazu and colleagues.[18] High doses of immunosuppressive agents augment the risk of infection, the development of malignancy, and organ toxicity. In our study, 10 of the 11 allograft recipients treated with low-dose cyclosporine (10 mg/kg/day) were protected from rejection, despite the fact that the dose was given on alternate days starting 101 days after transplantation. Thus it appears that even in the pig, short intestinal allografts require low doses of immunosuppression to prevent rejection.

The final immunologic advantage to the use of segmental intestinal grafts will only become evident with the routine clinical application of this therapy for the treatment of human short-gut syndrome. It is anticipated that the use of living related donors would provide closer HLA matching, thereby lessening the need for vigorous immunosuppression and presumably providing for improved results, as has been the experience with living related donor renal and pancreas transplantation. In addition this would decrease the demand for cadaveric organs. Finally the abdominal cavity of potential recipients who have been subjected to previous laparotomy might tolerate the addition of only a limited-sized viscus within its confines. It goes without saying that pediatric recipients' smaller abdominal cavities will not tolerate inclusion of total-length adult intestinal grafts.

Opponents of the use of segmental jejunal intestinal transplants might argue that the recipients are provided with only limited absorptive surface, which is deficient in its ability to absorb vitamin B_{12}, fats, and bile acids. There are many experimental and clinical studies that document the profound compensatory ability of residual small intestine after massive bowel resection.[19–21] We have demonstrated that rat segmental intestinal allografts demonstrate functional and structural alterations within 25 days after transplantation.[22] Similarly, by 150 days, the diameter of allotransplanted bowel increased by 267% in comparison to the preoperative bowel diameter.[7] Furthermore, as documented in the current study in pigs, segmental intestinal allografts maintain their compensatory ability and hypertrophy after massive reduction of the small bowel mass. Disruption of the enterohepatic circulation, due to presumed diminution of absorption of bile acids by the absence of ileal mucosa, did not result in gallstone formation in any of the recipients up to 180 days after transplantation. Finally megaloblastic anemia resulting from vitamin B_{12} deficiency was easily prevented by intramuscular vitamin supplementation.

Recent advances in overcoming the difficulties associated with small intestine transplantation may enable the establishment of this procedure as an efficacious therapy of short-gut syndrome. However concern remains as to the functional capabilities of the extrinsically denervated intestinal grafts. Ballinger et al.[23] discovered that autotransplantation of the small intestine in dogs resulted in weight loss, protracted diarrhea, decreased absorption of fat, and loss of mucosa and villi. These changes were not due to acute or chronic ischemia or to failure of lymphatic regeneration because denervation of the small intestine without ischemia produced changes identical to those observed after autotransplantation. Both isografts and nonrejecting allografts apparently absorb less water and electrolytes than does the normal bowel. In some instances this resulted in massive diarrhea capable of causing death. The role of extrinsic gut denervation in this altered absorptive function requires further elucidation. While some investigators have postulated that loss of inhibitory fibers markedly encourages bowel motility and transit of intraluminal content,[24–26] others have claimed that transplanted intestine has diminished myoelectrical activity, resulting in impaired motility.[27] In contrast Tapper has emphasized the local modulating ability of enteric neurons on intestinal ion transport.[28] In the present study allograft recipients suffered from some initial postoperative diarrhea that resolved within 2 weeks after transplantation. We have assumed that this increased passage of water and electrolytes was due to the initial posttransplant mucosal ischemic damage rather than to extrinsic denervation. At the time of death, none of the long-term survivors had any serum electrolyte abnormalities. Using a rat model of isograft transplantation, we have previously demonstrated that extrinsic denervation of the small intestine, as with transplantation, had no effect on glucose, maltose,[22] or cyclosporine absorption,[29] bowel wall content of vasoactive intestinal polypeptide,[30] intraluminal secretion of serotonin and substance P, or intraluminal release of serotonin in response to a hyperosmolar stimulus.[31]

The implied technical difficulties associated with the anastomoses of relatively small-caliber vessels required for segmental jejunal transplantation might negate the immunologic benefits and the absorptive compensatory capabilities of this approach. In addition the smaller-diameter vascular anastomoses might be more prone to spontaneous thrombosis as a consequence of the activation of the complement cascade and the infiltration of platelets as a component of the rejection process. In this study the jejunal artery and vein (as opposed to the superior mesenteric vessels) served as the vascular supply to the jejunal segment. Although the first four animals died due to vascular thrombosis of the graft, this was followed by 12 consecutive technical successes. Thus the jejunal artery and vein appear to be of sufficient caliber in pigs to allow for technically successful vascular anastomoses. In humans esophageal reconstruction after resection has been routinely performed using segmental intestinal autografts employing the jejunal artery and vein as the vascular supply.

Porcine short segment jejunal allograft recipients treated with only low-dose cyclosporine had significantly improved morbidity and mortality rates after total small bowel resection. Our results are testimony to the prophetic words of Ruiz and Lillehei who stated that "when intestinal allotransplantation is used to maintain nutrition in man, there would seem to be no need to use the entire small intestine of a cadaver; 1–2 meters should be sufficient. This type of intestinal allotransplantation deserves further trial."[32]

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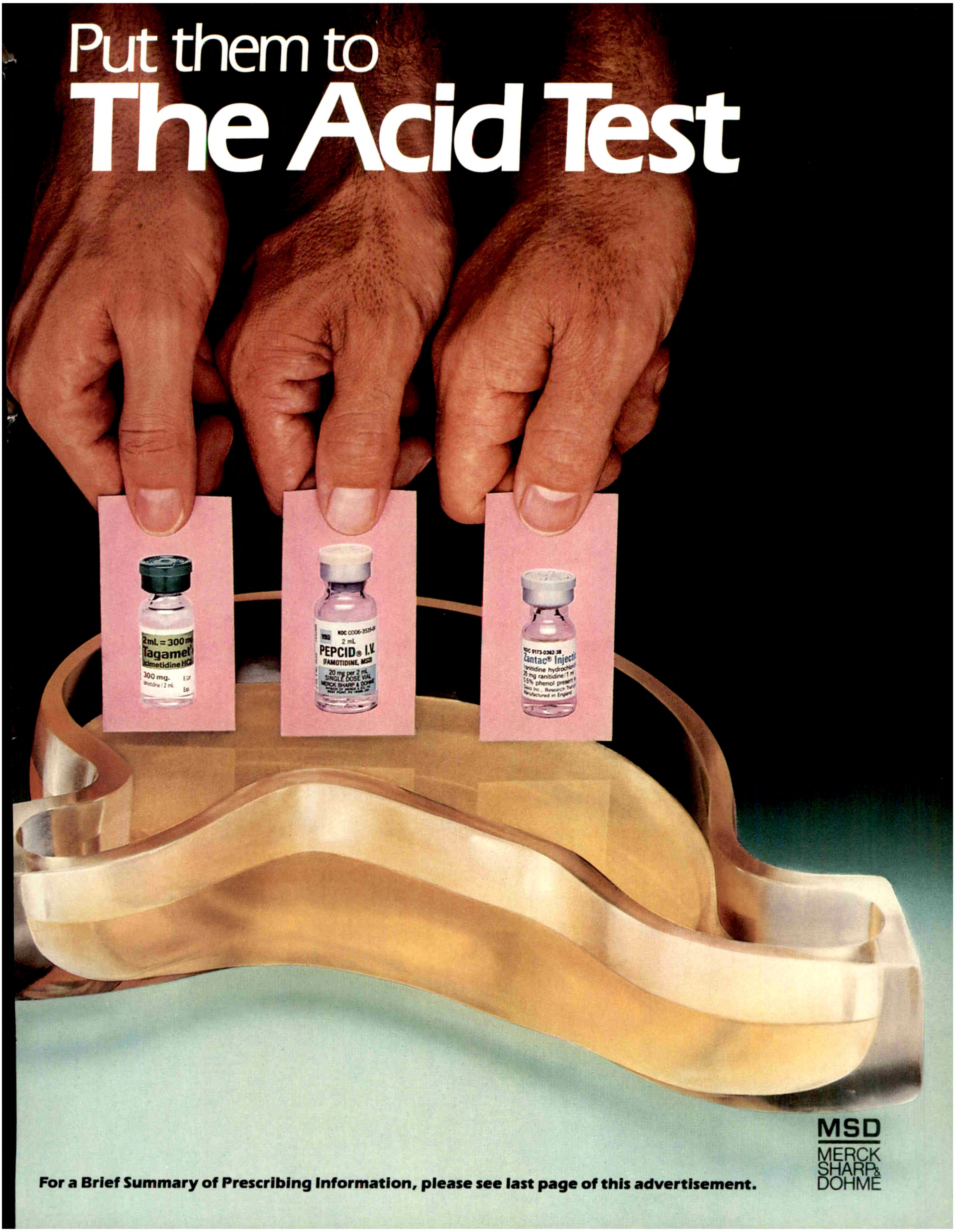

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PEPCID® I.V. (Famotidine, MSD) is indicated in some hospitalized patients with pathological hypersecretory conditions or intractable ulcers or as an alternative to the oral dosage forms for short-term use in patients who are unable to take oral medication.

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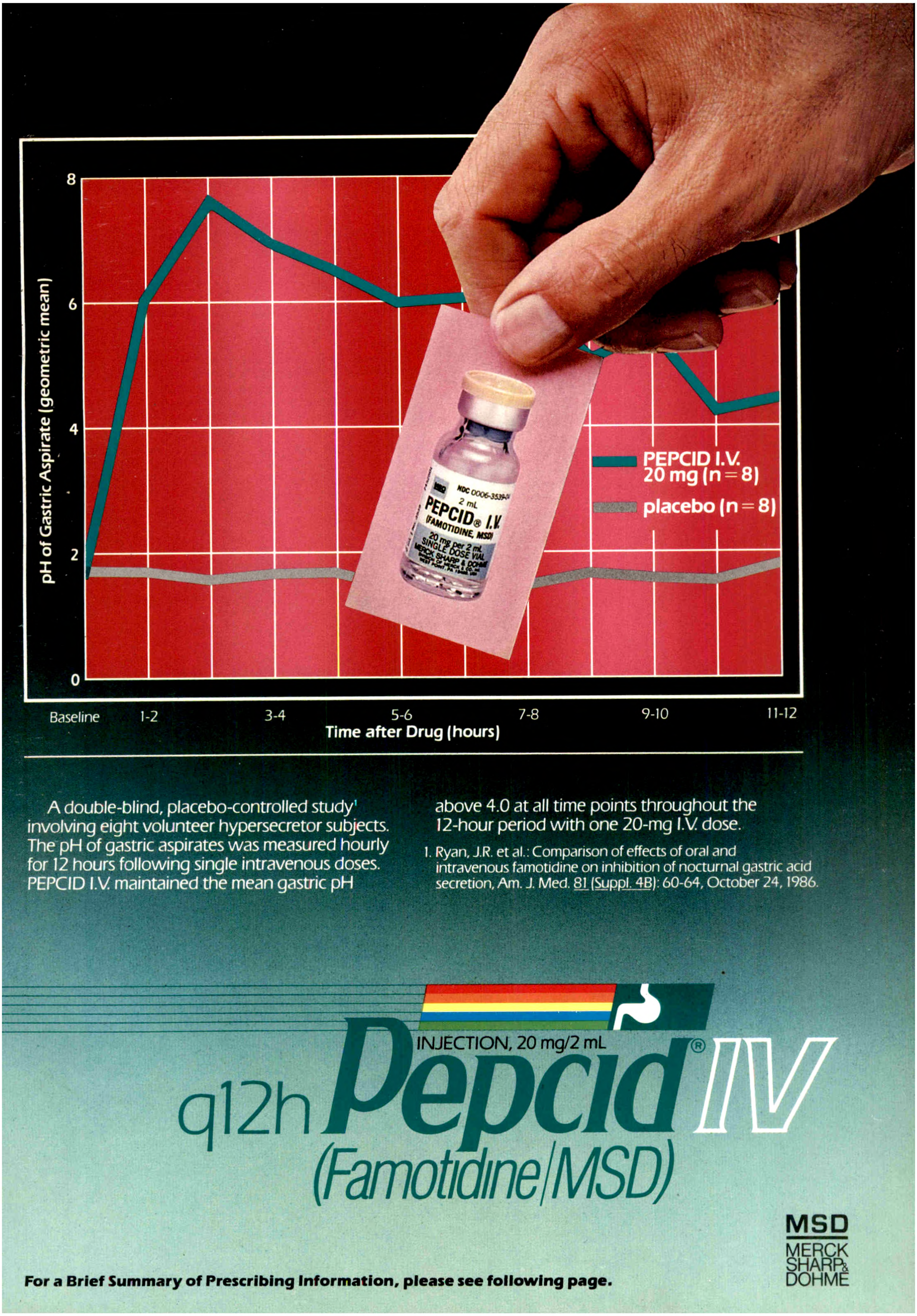

A double-blind, placebo-controlled study[1] involving eight volunteer hypersecretor subjects. The pH of gastric aspirates was measured hourly for 12 hours following single intravenous doses. PEPCID I.V. maintained the mean gastric pH above 4.0 at all time points throughout the 12-hour period with one 20-mg I.V. dose.

1. Ryan, J.R. et al.: Comparison of effects of oral and intravenous famotidine on inhibition of nocturnal gastric acid secretion, Am. J. Med. 81 (Suppl. 4B): 60-64, October 24, 1986.

INJECTION, 20 mg/2 mL

q12h **Pepcid® IV**

(Famotidine|MSD)

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Patients with Severe Renal Insufficiency: Longer intervals between doses or lower doses may be needed in patients with severe renal insufficiency (creatinine clearance <10 mL/min) to adjust for the longer elimination half-life of famotidine (see Clinical Pharmacology and Dosage and Administration sections of Prescribing Information).

Information for Patients: The oral suspension should be shaken vigorously for 5 to 10 seconds prior to each use, and unused constituted oral suspension should be discarded after 30 days.

Drug Interactions: No drug interactions have been identified. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine, and antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In rats and mice given oral doses up to approximately 2,500 times the recommended human dose for active duodenal ulcer, there was no evidence of carcinogenic potential; at these doses in rats, fertility and reproductive performance were not affected. No evidence of a mutagenic effect was observed.

Pregnancy: *Pregnancy Category B*—There are no adequate or well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether famotidine is secreted into human milk; however, it is secreted into the milk of lactating rats. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: No dosage adjustment is required based on age but may be necessary in severe renal impairment (see Clinical Pharmacology section of Prescribing Information).

Adverse Reactions: The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2,500 patients. In the placebo-controlled clinical trials, the incidence of adverse experiences with PEPCID Tablets 40 mg at bedtime was similar to that with placebo.

Incidence Greater than 1%: The following adverse reactions have been reported to occur in more than 1% of patients on therapy with PEPCID in controlled clinical trials and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%), and diarrhea (1.7%).

Causal Relationship Unknown: The following other adverse reactions have been reported infrequently and within each category are listed in order of decreasing severity. The relationship to therapy with PEPCID has been unclear in many cases. *Body as a Whole*—Fever, asthenia, fatigue. *Cardiovascular*—Palpitation. *Gastrointestinal*—Cholestatic jaundice, liver enzyme abnormalities, vomiting, nausea, abdominal discomfort, anorexia, dry mouth. *Hematologic*—Pancytopenia, leukopenia, thrombocytopenia. *Hypersensitivity*—Anaphylaxis, angioedema, orbital or facial edema, urticaria, rash, conjunctival injection. *Musculoskeletal*—Musculoskeletal pain, arthralgia. *Nervous System/Psychiatric*—Grand mal seizure; reversible psychic disturbances including hallucinations, confusion, agitation, depression, anxiety, decreased libido; paresthesia; insomnia; somnolence. *Respiratory*—Bronchospasm. *Skin*—Alopecia, acne, pruritus, dry skin, flushing. *Special Senses*—Tinnitus, taste disorder.

The adverse reactions reported for PEPCID Tablets may also occur with PEPCID Oral Suspension or PEPCID I.V.; in addition, transient irritation at the injection site has been observed with PEPCID I.V.

AV block has been reported with other H_2-receptor antagonists, but not with famotidine.

Management of Overdosage: There is no experience to date with deliberate overdosage. Up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

Dosage and Administration: ***Duodenal Ulcer:*** The recommended adult oral dosage for active duodenal ulcer is 40 mg h.s.; most patients heal within 4 weeks, and it is rarely necessary to use the full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective. For maintenance therapy, the recommended oral dosage is 20 mg h.s.

Benign Gastric Ulcer: The recommended adult oral dosage for active benign gastric ulcer is 40 mg h.s.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas): The dosage varies with the individual patient; the recommended adult oral starting dosage is 20 mg q6h, but some patients may require a higher starting dosage. Dosages should be adjusted to individual patient needs and continued as long as clinically indicated; up to 160 mg q6h have been administered to some patients with severe Zollinger-Ellison syndrome.

Oral Suspension: The oral suspension may be substituted for tablets.

Directions for Preparing PEPCID Oral Suspension: Prepare suspension at time of dispensing. Slowly add 46 mL Purified Water. Shake vigorously for 5 to 10 seconds immediately after adding the water and immediately before use.

Stability of PEPCID Oral Suspension: Unused constituted oral suspension should be discarded after 30 days.

Intravenous Administration: In some hospitalized patients with pathological hypersecretory conditions or intractable ulcers or in patients who are unable to take oral medication, the recommended intravenous dosage is 20 mg q12h. For preparation of intravenous solutions for injection or infusion and for compatible diluents, please see Prescribing Information. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Concomitant Use of Antacids: Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Severe Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance less than 10 mL/min), the elimination half-life of famotidine may exceed 20 hours, reaching approximately 24 hours in anuric patients. Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dosage may be reduced to 20 mg h.s. or the dosing interval may be prolonged to 36 to 48 hours as indicated by the patient's clinical response.

How Supplied: Tablets, containing 20 mg or 40 mg famotidine, with hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide as inactive ingredients, in unit-of-use bottles of 30 and unit-dose packages of 100; Oral Suspension, containing 40 mg famotidine per 5 mL after constitution with 46 mL Purified Water, with citric acid, flavors, microcrystalline cellulose and carboxymethylcellulose sodium, sucrose, and xanthan gum as inactive ingredients, and sodium benzoate 0.1%, sodium methylparaben 0.1%, and sodium propylparaben 0.02% added as preservatives, in bottles of 400 mg famotidine for constitution; Solution for intravenous injection, containing 10 mg famotidine per mL, with L-aspartic acid 4 mg, mannitol 20 mg, and Water for Injection q.s. 1 mL as inactive ingredients, and benzyl alcohol 0.9% added as preservative to the multidose vial, as 10x2-mL single-dose vials and as 4-mL vials.

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The Bacteriology of Gangrenous and Perforated Appendicitis—Revisited

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By using optimum sampling, transport, and culture techniques in patients with gangrenous or perforated appendicitis, we recovered larger numbers of bacteria with a more diverse flora than has previously been reported. Thirty patients older than 12 years with histologically documented gangrenous or perforated appendicitis had peritoneal fluid, appendiceal tissue, and abscess contents (if present) cultured. Appendiceal tissue was obtained so as to exclude the lumen. A total of 223 anaerobes and 82 aerobic or faculatative bacteria were recovered, an average of 10.2 different organisms per specimen. Twenty-one different genera and more than 40 species were encountered. *Bacteroides fragilis* group and *Escherichia coli* were isolated from almost all specimens. Within the *B. fragilis* group, eight species were represented. Other frequent isolates included *Peptostreptococcus* (80%), *Pseudomonas* (40% [*P. aeruginosa*, 23.3%, other *Pseudomonas* spp., 16.7%]), *B. splanchnicus* (40%), *B. intermedius* (36.7%), and *Lactobacillus* (36.7%). Interestingly a previously undescribed fastidious gram-negative anaerobic bacillus was isolated from nearly one half of all patients. This organism was found to have low DNA homology (by dot blot) with the known organisms most closely resembling it.

IN 1938 ALTEMEIER reported an outstanding study documenting the polymicrobial nature of the flora in perforated appendicitis.[1] Anaerobic transport and culturing techniques have improved during the intervening years, and taxonomy has changed considerably; nevertheless little progress has been made in the recovery of specific isolates since this landmark report. The current study was designed to attempt to definitively elucidate the specific microbiology of gangrenous and perforated appendicitis using optimal culturing and identification techniques.

Patients and Methods

Thirty patients older than 12 years with a histologically proved diagnosis of gangrenous or perforated appendicitis comprise the study population. All patients were operated on at the Olive View Medical Center between December 1987 and October 1988, and had had neither recent hospitalizations nor parenteral antibiotic therapy before this admission. Once the diagnosis of appendicitis was established, all patients were given nothing by mouth, started on intravenous fluids and antibiotics (either a second- or third-generation cephalosporin as part of an ongoing double-blind study), and taken expeditiously to the operating room. The time between administration of the antibiotic and surgery ranged from 30 to 185 minutes. All operations were performed through a right lower quadrant, muscle-splitting, transverse incision. Samples of peritoneal fluid, abscess contents, and appendiceal tissue were collected as described below. Appendectomy was performed on all patients and any loculated intra-abdominal fluid collections were drained. The peritoneal cavity was always irrigated with normal saline and the wound was closed in layers. The skin was loosely approximated unless frankly purulent material was present, in which case it was packed open to heal by secondary intent.

Specimen Procurement

If free peritoneal fluid was present, it was aspirated into a syringe immediately on entering the abdominal cavity.

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In those instances in which a definite abscess was present, material for culture was obtained from the abscess with a needle and syringe. Early in the course of the study, some peritoneal fluid specimens in patients with gangrenous appendicitis failed to yield organisms. Therefore the protocol was changed so that appendiceal tissue as well as peritoneal fluid was collected from each patient. This necrotic appendiceal tissue was obtained by tangentially cutting a narrow slice from the area of necrosis, carefully avoiding the lumen (documented histologically). From 21 patients, both peritoneal fluid and appendiceal tissue were processed simultaneously to compare bacterial recovery quantitatively and qualitatively.

Specimen Transportation and Culture

Fluid specimens were injected into an anaerobic transport vial (Port-a-Cul vial, BBL Microbiology Systems, Cockeysville, MD) and tissue biopsies were placed in a sterile snap-top plastic tube (17 × 100 mm Falcon tubes, Becton-Dickinson, Oxnard, CA), which was immediately sealed in a self-generating anaerobic pouch (GasPak pouch, BBL). The caps of the tubes were left loose until the methylene blue indicator in the pouch indicated anaerobic conditions, at which time the cap was snapped closed to prevent dehydration of the tissue. Specimens were held at room temperature until they were transported to the Wadsworth Anaerobic Laboratory and inoculated, usually within 18 hours of collection.

Specimen manipulations were carried out in an atmosphere of 80% nitrogen, 10% carbon dioxide, and 10% hydrogen within an anaerobic chamber (Coy Laboratory Products, Ann Arbor, MI). Tissue specimens were ground in plastic disposable tissue grinders (Sage Products, Cary, IL) in measured amounts of liquid thioglycollate medium. Measured quantities of vortexed tissue suspensions or fluid specimens were inoculated onto supplemented Brucella blood agar, phenylethyl alcohol agar, kanamycin-vancomycin agar with laked sheep blood, Bacteroides bile esculin agar, and into supplemented thioglycollate broth (Anaerobe Systems, Santa Clara, CA) in addition to routine aerobic media.[2] All anaerobic media used were of the prereduced and anaerobically sterilized (PRAS) variety. Initial anaerobic incubation took place in the chamber at 35 C. Plates were examined after a minimum of 48 hours of incubation and on additional occasions for up to ten days. All colony morphotypes seen on each agar were isolated for further studies. Thioglycollate broths were subcultured only if plate media yielded no growth.

Biochemical Characterization

After initial isolation, the culture plates were examined in air, subcultured as indicated, and promptly incubated in anaerobic GasPak jars (BBL Microbiology Systems). The identification procedures used were those described in the Wadsworth and VPI Anaerobe Manuals.[2,3] Preliminary tests included inhibition by special potency antibiotic disks (vancomycin, 5 mcg; kanamycin, 1000 mcg; and colistin, 10 mcg [BBL Microbiology Systems]), inhibition by 20% bile disks (Remel, Lenexa, KS), catalase production (30% H_2O_2), and spot indole and nitrate reactions (N,N tetramethyl aminocinnamaldehyde and nitrate disks; Anaerobe Systems). Hydrogen sulfide production was detected in SIM medium (BBL Microbiology Systems). Urease production was detected in urease broth concentrate (Difco Laboratories, Detroit, MI) diluted 1:10. Lecithinase and lipase production were determined on freshly prepared egg yolk agar, and the ethanol test was used to check for spore formation. Motility was studied by the hanging drop method, and fermentation reactions and metabolic endproducts, nitrate reduction, indole production, bile stimulation, and esculin and gelatin hydrolysis were carried out in PRAS media (Carr-Scarborough Microbiologicals, Stone Mountain, GA). All broth media were supplemented as necessary, using standard methods.

Gas-Liquid Chromatography

Volatile and nonvolatile products of metabolism were determined by standard methods on the Varian Aerograph gas-liquid chromatograph (Varian, Palo Alto, CA) using a 1220/H_2PO_4 packed metal column (Supelco, Bellefonte, PA) and either a thermal conductivity detector or a flame ionization detector as previously described.[2]

Results

In this group of 30 patients with documented gangrenous or perforated appendicitis, there were 26 male and 4 female individuals whose mean age was 26.6 years (range, 12 to 63 years). All patients reported right lower quadrant abdominal pain with a mean duration of 58.1 hours. This and other relevant patient-related information is summarized in Table 1. There were no significant dif-

TABLE 1. *Stratification of Patients with Gangrenous and Perforated Appendicitis*

Patient Data	Gangrene (n = 12)	Perforation (n = 18)	All (n = 30)
Mean age (yrs.)	25.4	27.3	26.6
Sex (M/F)	10/2*	16/2*	26/4*
Mean duration of abdominal pain (hrs.)	40.0	71.7	58.1
Mean length operation (hrs.)	1.0	1.3	1.2
Admission temperature (C)	38.4	38.7	38.5
Admission WBC (10^9/L)	15.3	16.9	16.2
Nausea	8	14	22
Vomiting	6	10	16

* $p < 0.001$ (men *vs.* women, all groups).

TABLE 2. *Number of Different Bacteria Isolated from Patients with Gangrenous and Perforated Appendicitis*

Bacteria	Gangrene (n = 12) Number; Mean	Perforated (n = 18) Number; Mean	All (n = 30) Number; Mean
Aerobes	29; 2.4	53; 2.9	82; 2.7
Anaerobes	76; 6.3	147; 8.2	223; 7.4
Total	105; 8.8	200; 11.1	305; 10.2

ferences between patients with gangrenous appendicitis and those with perforated appendicitis for those parameters listed.

At operation it was found that 18 of the patients had perforated appendicitis, while the remaining 12 patients had gangrenous appendicitis. All patients underwent appendectomy; in nine of the patients with perforated appendicitis (50%), a loculated intra-abdominal abscess was drained through a separate stab wound in the abdominal wall. In all patients with perforated appendicitis the skin was left open for healing by secondary intent, while in those patients with gangrenous appendicitis the skin was closed loosely. There were no deaths and only one complication, a recurrent intra-abdominal abscess three days after operation in a patient whose initial operation had been for perforated appendicitis with abscess formation. A reoperation was required to drain this recurrent abscess. All patients have done well on follow-up ranging from 6 to 15 months.

Bacteriologic Findings

The mean time from collection of the specimen and inoculation and processing was 15.9 hours (range, 1.3 to 41.7 hours), and bacteria grew in specimens collected from all patients. The number of aerobic organisms isolated ranged from zero (in two specimens) to six per specimen, while from 1 to 13 different anaerobic organisms were isolated per specimen. Table 2 summarizes the total number of different aerobic and anaerobic bacteria isolated, as well as the mean number of individual aerobes and anaerobes grown from these patients with gangrenous appendicitis and perforated appendicitis. There was no significant difference between the number of different bacterial isolates from patients with gangrenous appendicitis and those with perforated appendicitis. In those cases in which both free peritoneal fluid and an abscess were encountered, it was found that the same organisms grew from both. Tables 3 and 4 summarize the actual aerobic and anaerobic organisms isolated, by genus and species. In 35 of the 46 different species groups indicated (76.1%), moderate to heavy bacterial growth (as quantified as 3+ to 4+ of 4+) was encountered in most instances.

In the early phases of specimen collection, it was noted that the peritoneal fluid in patients with frankly gangrenous or necrotic appendices without perforation would grow bacteria only sporadically. It was therefore decided to process both peritoneal fluid and a sample of necrotic appendiceal tissue in all patients. This sample of appendiceal tissue consisted of a tangential slice through the area of necrosis taking care not to enter the lumen (this was documented microscopically). The ten appendiceal specimens procured in this way from patients with gangrenous appendicitis all grew bacteria. Concurrent peritoneal fluid specimens in three of these ten instances grew the same organisms. In the other seven specimens there was no growth. Bacteria were cultured from both the appendiceal tissue and peritoneal fluid specimens in the 11 patients with perforated appendicitis in which both samples were collected. The flora was the same in both types of specimens in these patients.

Appendiceal tissue and peritoneal fluid from three additional patients with grossly normal appendices were processed in the same manner. The peritoneal fluid cultures and two of the appendiceal tissue specimens in these

TABLE 3. *Aerobic and Facultative Bacteria Cultured from Patients with Gangrenous and Perforated Appendicitis*

Bacteria	Gangrenous (%) (n = 12)	Perforated (%) (n = 18)	All (%) (n = 30)
Escherichia coli	11 (91.7)	14 (77.8)	25 (83.3)
Viridans streptococci	4 (33.3)	6 (33.3)	10 (33.3)
Pseudomonas aeruginosa	2 (16.7)	5 (27.8)	7 (23.3)
Streptococcus, group D	1 (8.3)	5 (27.8)	6 (20.0)
Pseudomonas spp.	1 (8.3)	4 (22.2)	5 (16.7)
β-hemolytic Streptococcus, group F	1 (8.3)	3 (16.7)	4 (13.3)
Enterococcus spp.	2 (16.7)	2 (11.1)	4 (13.3)
Citrobacter freundii	0 (0)	2 (11.1)	2 (6.7)
β-hemolytic Streptococcus, group C	1 (8.3)	1 (5.6)	2 (6.7)
Staphylococcus aureus	1 (8.3)	1 (5.6)	2 (6.7)
Enterobacter cloacae	1 (8.3)	0 (0)	1 (3.3)
β-hemolytic Streptococcus, group G	0 (0)	1 (5.6)	1 (3.3)
Corynebacterium spp.	0 (0)	1 (5.6)	1 (3.3)
Moraxella spp.	1 (8.3)	0 (0)	1 (3.3)

TABLE 4. *Anaerobic Bacteria Cultured in Patients with Gangrenous and Perforated Appendicitis*

Bacteria	Gangrenous (%) (n = 12)	Perforated (%) (n = 18)	All (%) (n = 30)
Bacteroides fragilis	7 (58.3)	15 (83.3)	22 (73.3)
Bacteroides thetaiotaomicron	6 (50.0)	15 (83.3)	21 (70.0)
Peptostreptococcus micros	4 (33.3)	13 (72.2)	17 (56.7)
Bilophila wadsworthia	4 (33.3)	10 (55.6)	14 (46.7)
Bacteroides splanchnicus	5 (41.7)	7 (38.9)	12 (40.0)
Bacteroides intermedius	4 (33.3)	7 (38.9)	11 (36.7)
Lactobacillus spp.	4 (33.3)	7 (38.9)	11 (36.7)
Bacteroides ovatus	2 (16.7)	8 (44.4)	10 (33.3)
Bacteroides vulgatus	3 (25.0)	7 (38.9)	10 (33.3)
Fusobacterium spp.	4 (33.3)	6 (33.3)	10 (33.3)
Eubacterium spp.	4 (33.3)	6 (33.3)	10 (33.3)
Bacteroides distasonis	3 (25.0)	5 (27.8)	8 (26.7)
Bacteroides uniformis	4 (33.3)	3 (16.7)	7 (23.3)
Peptostreptococcus spp.	4 (33.3)	3 (16.7)	7 (23.3)
*Microaerophilic streptococci**	3 (25.0)	4 (22.2)	7 (23.3)
Actinomyces spp.	1 (8.3)	4 (22.2)	5 (16.7)
Bacteroides gracilis	1 (8.3)	3 (16.7)	4 (13.3)
Clostridium clostridiiforme	1 (8.3)	3 (16.7)	4 (13.3)
Clostridium ramosum	1 (8.3)	3 (16.7)	4 (13.3)
Bacteroides buccae	0 (0)	3 (16.7)	3 (10.0)
Bacteroides caccae	0 (0)	2 (11.1)	2 (6.7)
Clostridium innocuum	0 (0)	2 (11.1)	2 (6.7)
Porphyromonas spp.	2 (16.7)	0 (0)	2 (6.7)
Bacteroides oris	0 (0)	1 (5.6)	1 (3.3)
Bacteroides oralis	0 (0)	1 (5.6)	1 (3.3)
Bacteroides stercoris	0 (0)	1 (5.6)	1 (3.3)
Bacteroides denticola	0 (0)	1 (5.6)	1 (3.3)
Clostridium leptum	1 (8.3)	0 (0)	1 (3.3)
Clostridium sporogenes	0 (0)	1 (5.6)	1 (3.3)
Desulfomonas pigra	0 (0)	1 (5.6)	1 (3.3)
Mitsuokella multiacida	0 (0)	1 (5.6)	1 (3.3)
Propionibacterium acnes	1 (8.3)	0 (0)	1 (3.3)
Unidentified gram − rod	2 (16.7)	2 (11.1)	4 (13.3)
Unidentified gram + rod	1 (8.3)	1 (5.6)	2 (6.7)
Unidentified pigmenting rod	1 (8.3)	0 (0)	1 (3.3)

* Not true anaerobes, but placed here because good anaerobic transport and culture techniques are often required for their recovery.

three grew nothing, while one tissue specimen grew only a few colonies of *E. coli*, *Staphylococcus* spp., and *B. vulgatus.*

Interestingly we encountered a previously undescribed anaerobic bacterium in nearly one half of the patients (Table 4). It is a fastidious, nonmotile, gram-negative bacillus. It is 0.9 × 1 to 12 μm in size, and is strongly catalase positive, urease positive, H_2S and NO_3 positive, asaccharolytic, stimulated by bile and pyruvate, and is not a sulfate reducer. Its major metabolic end-product is acetic acid, with a trace of succinic acid at times. Cellular fatty acids and genetic make-up are distinct from those of known organisms most closely resembling it. We propose the name *Bilophila wadsworthia* for this organism.

Discussion

More than 50 years ago Altemeier elucidated the startling (at that time) fact that the fluid encountered during surgery to treat perforated appendicitis with peritonitis yielded multiple aerobic and anaerobic organisms on culture.[1] Although both aerobic and anaerobic bacteria had been identified previously in the peritoneal fluid of patients with perforated appendicitis,[4–8] these collections were generally thought to represent cultures of either a single organism or only a couple of organisms together. With the observations that aerobic and anaerobic organisms can frequently occur together and work in synergy to increase the pathogenicity of the infectious process,[9,10] a fairly complete understanding of the bacteriology of complex intra-abdominal infections had been brought about.

Whereas 50 years ago Altemeier isolated slightly more than four organisms per specimen,[1] improvements in specimen handling and culture techniques, as well as the subsequent description of many "new" organisms (especially among the anaerobes), should have led to an increase in the number of organisms recovered from patients with gangrenous or perforated appendicitis. Surprisingly, however, the number of organisms recovered from the intraoperative cultures of these patients has not increased. Table 5 lists recent reports from the literature showing the number of aerobic and anaerobic bacteria isolated from patients with gangrenous or perforated appendicitis. As shown a mean of 1.2 aerobes and 0.9 anaerobes per specimen, actually less than Altemeier obtained, was recovered. Our report is significantly different from those previously described and provides new insight into the complexity and diversity of the bacteriology of appendicitis.

The quantity and diversity of the organisms we recovered in this study of gangrenous and perforated appendicitis (Tables 3 and 4) is not very surprising considering the large number of bacteria within the colon.[20] We recovered more than 20 genera and 40 species, and our findings of *E. coli* as the most frequently encountered aerobe and *B. fragilis* as the most frequently recovered anaerobe agree with previous reports in patients with gangrenous and perforated appendicitis. However while our recovery of most other aerobic and facultative bacteria (*Pseudomonas, Enterobacter,* and so on) was similar to other studies, we found viridans streptococci more frequently and enterococcus less frequently [18,23] The plethora of anaerobes isolated was noteworthy, especially the large numbers of members of the *B. fragilis* group. We were surprised at the number of specimens found to contain the new anaerobic bacillus *Bilophila wadsworthia,* and anticipate further work to fully elucidate the nature and pathogenicity of this organism. This organism is of potential importance in that it was the fourth most common anaerobe (and fifth most common isolate overall), and is more resistant to antimicrobial agents than members of the *B. fragilis* group. Our studies (to be reported elsewhere) show significant resistance (52% to 67% of strains) to cefoxitin, imipenem, penicillin G, and piperacillin. As in previous reports,[11,13,17,18] the number of specimens containing *Clostridium* is relatively small, although our isolation of *Lactobacillus, Fusobacterium,* and *Eubacterium* in one third or more of the specimens is greater than other reports.[11,13,24]

TABLE 5. *Reported Frequency of Bacteria Isolated from Patients with Gangrenous and Perforated Appendicitis in the Literature*

Study	Aerobes (Mean)	Anaerobes (Mean)	All (Mean)
Brook, 1980[11] (n = 112)	144 (1.4)	301 (2.7)	445 (4.0)
David et al., 1982[12] (n = 300)	430 (1.4)	127 (0.4)	557 (1.9)
Pieper et al., 1982[13] (n = 31)	61 (2.0)	89 (2.9)	150 (4.8)
Berne et al., 1982[14] (n = 130)	101 (0.8)	88 (0.7)	189 (1.5)
King et al., 1983[15] (n= 63)	80 (1.3)	59 (0.9)	139 (2.2)
Elhag et al., 1986[16] (n = 101)	90 (0.9)	106 (1.0)	196 (1.9)
Berne et al., 1987[17] (n = 162)	130 (0.8)	91 (0.6)	221 (1.4)
Bennion et al., 1987[18] (n = 68)	96 (1.4)	29 (0.4)	125 (1.8)
Jakobsen et al., 1988[19] (n = 93)	113 (1.2)	65 (0.7)	178 (1.9)
Total (n = 1060)	1245 (1.2)	955 (0.9)	2200 (2.1)

Comparison of our report with previous studies on normal gut flora from our laboratory[20] revealed the relative frequency of most aerobic and facultative bacteria (*e.g., E. coli,* viridans streptococci, most other streptococcal species, *S. aureus,* and so on) to be the same. However the recovery of enterococci and *Enterobacter cloacae* in patients with gangrenous and perforated appendicitis was much less frequent than normal, whereas *Pseudomonas* spp., especially *P. aeruginosa,* were found more frequently. Among the anaerobic bacteria, *Lactobacillus* spp., *Eubacterium* spp., *B. vulgatus, B. distasonis,* and *Clostridium ramosum* were decreased in frequency in appendicitis, while *B. fragilis, B. splanchnicus, Peptostreptococcus micros,* and *Fusobacterium* spp. were found more frequently. Interestingly we never recovered *C. perfringens* from these appendicitis patients, although it was found in nearly 50% of normal gut flora specimens. These changes in the relative frequency of bacteria present in these patients with gangrenous or perforated appendicitis may have implications as to the relative pathogenicity of the individual organisms in appendicitis.

Our decision to culture the appendiceal wall, in addition to routine peritoneal fluid cultures, was based on previous experimental observations that progressive bacterial invasion of intestinal tissue occurs with increasing visceral ischemia and breakdown of the mucosal barier.[21,22] Lau et al.[23] have demonstrated in the clinical setting that bacterial infection advances through the appendicular wall as the disease progresses in patients with varying degrees of appendicitis. We believe that the procurement of appendiceal tissue specimens for culture should be obtained in such a way as to avoid entrance into the lumen. In some previously reported studies, the appendix was bisected to obtain specimens for culture,[13,24,25] thereby insuring a culture of normal luminal contents. We believe that histologically documented absence of luminal penetration is the best method to prevent the culturing of normal bowel flora. Our method should recover only invasive pathogens within the tissue. The culturing of luminal contents may well be the reason why Roberts[25] recently reported no differences between the flora of histologically normal and inflamed appendices.

We were gratified by our ability to recover so many more organisms than had been previously reported in appendicitis despite transport over a distance of more than 20 miles and intervals of up to 42 hours. Our method of immediate placement of the specimens taken at operation into either an anaerobic transport vial or a self-generating anaerobic pouch is neither new nor unique. Such a practice was used by the majority of authors cited in Table 5.[11,13,14,17,18] Perhaps some delay in the placing of specimens under anaerobic conditions was encountered at times by other investigators. In addition the existence of a possible difference in the effectiveness of available transport systems might also explain the discrepancy. There was one notable difference from our technique, though, in the work of Pieper et al.[13,24] in which they stored the anaerobic culture tube at 4 C before processing, whereas we routinely stored our samples at room temperature. Oxygen diffuses better at colder temperatures and could be a problem unless tubes are absolutely gas tight.

Since both Pieper et al.[13,24] and Elhag et al.[16] routinely cultured appendiceal tissue and, it appears, luminal contents, and recovered far fewer isolates per specimen (from two to five) than we did, our recovery rate cannot be explained by the use of tissue for culture in addition to peritoneal fluid. More rapid transportation for plating of the specimens also does not explain this difference because it was not uncommon for our specimens to be processed 24 hours after collection, with no apparent decrease in quantity or diversity of isolates.

We believe that the explanation for our ability to recover more than ten different organisms per specimen in these patients with gangrenous or perforated appendicitis is multifaceted. First this laboratory has had a long-standing interest in elucidating the role of anaerobic bacteria in varied disease processes and is attuned to the complexities involved in isolation of these fastidious organisms, with particular attention being paid to specimen collection and transportation. Initial processing of the specimens is always performed in a strict anaerobic environment using true prereduced media (media never exposed to oxygen while being prepared and subsequently), which undoubtedly aids in the recovery of fastidious organisms. Whereas most hospital clinical laboratories have many different technicians processing numerous specimens from all sources, all the specimens in this study were processed by only three individuals (EJB, JD, PS) paying close attention to specific protocols developed by this laboratory.[2] In addition the recovery of large numbers of anaerobic organisms requires a great deal of time and patience, a luxury that some facilities, particularly clinical laboratories, may not have.

The clinical significance of this work remains to be completely elucidated and is the subject of our ongoing investigations. It is apparent, however, that the numbers and diversity of the organisms potentially recoverable from patients with gangrenous or perforated appendicitis greatly exceeds all previous reports. Whereas it is generally accepted that antimicrobial coverage should be directed only toward the most prevalent aerobes and/or anaerobes potentially present in the infectious process, our data may explain therapeutic failures. Less frequently encountered organisms that are very resistant (*e.g., Bilophila*) could be the source of such failure despite what is believed to be adequate antibiotic coverage. Our only treatment failure in this group of patients (intra-abdominal abscess and continued sepsis) occurred in a patient in whom nonenterococcal Group D *Streptococcus* resistant to the antibiotic used was isolated.

The initial antimicrobial therapy of appendicitis must be empiric. The data from this study will serve as a guide to the usual bacteriology of such infections. This is important in that it will not be practical (in terms of the long time period before organisms, especially anaerobes, are obtained in pure culture and identified) or cost-effective for hospital laboratories to undertake such detailed studies for clinical purposes. The major aerobic and facultative bacteria can be recovered readily and rapidly. It may be reasonable, except in severely ill patients with intra-abdominal infections, to limit anaerobic cultures to a single medium (*e.g.,* Bacteroides bile esculin agar) that will grow the most prevalent and resistant flora (the *B. fragilis* group and *Bilophila*), or even to forego anaerobic cultures entirely.

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Cirrhosis in the Trauma Victim

Effect on Mortality Rates

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To evaluate the impact cirrhosis has on survival the records of 40 cirrhotic trauma victims from the registries of two Level 1 trauma centers were reviewed and probability of survival calculated using the TRISS methodology. Mechanism of injury, anatomic location, involvement of single or multiple sites, presence of ascites, elevations in serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase, serum bilirubin, prothrombin time (PT), and hypoalbuminemia were tabulated for each patient. Contingency tables were created for injury and hepatic parameters, as related to survival, and subjected to chi square analysis. Loglinear analysis was performed on all significant parameters to evaluate the independent effects of injury characteristics and hepatic insufficiency on survival. Predicted survival was 93%; observed survival was 70% ($Z = -6.92$; $p < 0.001$). Cause of death was multiple-system organ failure (9) and closed head injury (3). Admission markers of poor outcome included one or more of the following: ascites, elevated PT or bilirubin, history of motor vehicle accident, multiple trauma, or blunt abdominal trauma requiring laparotomy. Loglinear analysis revealed that the presence of ascites, elevated PT, or bilirubin, further diminished the rate of survival for any individual injury characteristic. We concluded that survival among cirrhotic trauma victims was significantly lower than predicted. In addition the presence of hepatic insufficiency further diminishes survival, regardless of the injury sustained.

HEPATIC CIRRHOSIS IS the predominant cause of death in approximately 30,000 patients each year.[1] It is the fifth leading cause of death in individuals aged 45 to 64 years.[2] Cirrhosis, as a comorbid factor, also contributes to the demise of many more patients.

Many reports have shown that patients with cirrhosis who undergo elective or emergency surgery have significantly increased mortality and morbidity rates.[3-15] Also the degree of hepatic insufficiency is a prime factor in determining outcome in these patients.

Despite interest in the outcome of the cirrhotic surgical patient, there are, to date, no reports regarding the outcome of cirrhotic patients after traumatic injury. This study reviews the experience at two trauma centers with cirrhotic patients who sustained various injuries and characterizes the effect of this premorbid state on their outcome.

Materials and Methods

Data on more than 27,000 patients admitted to the trauma service at Lehigh Valley Hospital Center and Allegheny General Hospital over a 9-year period are contained in their respective trauma registries. These data were analyzed for patients filed under the ICDM-3 index for chronic liver disease with cirrhosis (571.0). The trauma registry abstract and medical record of all patients with this diagnosis were reviewed. Diagnosis of hepatic cirrhosis was confirmed by past medical history, clinical exam, operative findings, biopsy, and/or imaging. Patients were characterized by age, sex, trauma score, injury severity score, mechanism of injury, and outcome. These profiles were then analyzed for predicted outcome as compared to observed outcome. Predicted outcome was calculated for each individual and the group using the TRISS probability of survival.[16]

Patients' injuries were further characterized by anatomic location and involvement of single or multiple sites. In addition evidence of hepatic insufficiency was evaluated by assessing admission data for the presence of ascites, hyperbilirubinemia (more than 2 mg/dL), hypoalbumin-

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emia (less than 3.5 mg/dL), elevations in alkaline phosphatase (more than 125 μ/L), serum glutamic oxaloacetic transaminase (SGOT more than 40 μ/L), and/or prothrombin time (more than 12.5 seconds). For both the above injury profile and hepatic insufficiency profile, contingency tables were created for presence or absence of each parameter as related to outcome. These were subjected to chi square analysis with the significance level set at $p < 0.05$. Stepwise loglinear analysis using BMDP4F[17] was performed on all selected parameters to assess the combined and individual effect of specific injury characteristics and hepatic insufficiency on survival.

Results

Forty patients (1.4 per 1000 trauma admissions) admitted to the trauma service at the Lehigh Valley Hospital Center (24 patients) and Allegheny General Hospital (16 patients) from January 1979 to June 1988 had evidence of hepatic cirrhosis on clinical pathologic, and/or radiologic grounds. In 35 patients the diagnosis was made before admission during previous hospitalization, or as an outpatient. Twenty-two patients had diagnostic biopsy and 13 patients had the diagnosis made on clinical grounds, confirmed by radiologic and laboratory evidence. The remaining five patients were diagnosed during exploratory laparotomy for traumatic injury (two patients) or at autopsy (three patients). In 33 patients the etiology of the cirrhosis was related to alcohol. In six patients cirrhosis was cryptogenic, although in one patient Methyldopa toxicity was suggested as an inciting factor. The remaining patient had primary biliary cirrhosis.

The demographic and outcome data for the whole group are contained in Table 1. Noteworthy is that the predicted survival as reflected by TRISS was significantly greater ($p < 0.05$) than the observed survival (93% *vs.* 70%) with an associated Z statistic of −6.92 and M statistic of 0.86.

Although the predominant mechanism of injury was accidental fall (Table 2), 58% (7 of 12) of deaths were due to motor vehicle accidents. Other mechanisms of injury included a superficial abdominal stab wound, a criminal assault, and a 30% total–body-surface area burn.

TABLE 1. *Demographic and Survival Data*

(n = 40)*	Range
Mean age = 58	31–84
Mean TS = 15	6–16
Mean ISS = 14	5–34
TRISS = 0.93	
Surv = 0.70†	

* There were 28 men and 12 women.

† $p < 0.05$ as compared to TRISS.

TABLE 2. *Mechanism of Injury*

Mechanism of Injury	Total	Nonsurvivors (%)
Fall	25	4 (14)
MVA	12	7 (58)
Other	3	1 (33)

Table 3 lists the injuries by anatomic location. Fifteen patients had evidence of head trauma (closed head injury or skull fracture). Six of these patients died. In three of these six patients, head injury was the predominant cause of death.

Seven patients sustained blunt thoracic trauma including rib fractures, pulmonary contusion, or hemopneumothorax. One patient had both EKG and echocardiographic evidence of myocardial contusion. All patients in this group, including nonsurvivors, had significant associated injuries.

Blunt abdominal trauma evidenced by hemoperitoneum, splenic rupture, and/or liver laceration was the predominant injury in nine patients. Eight patients underwent laparotomy. The remaining patient, a known cirrhotic, had computed tomographic evidence of a class I liver laceration and was observed. Six of these patients, including the patient who was observed, died.

Pelvic fractures or extremity long-bone fractures occurred in 25 patients. Although eight deaths occurred in this group, five patients had more serious associated injuries. In fact, of the 12 who sustained pelvic fracture or extremity long-bone fracture as the single site of injury, only two patients died, succumbing to hepatic failure after lengthy hospitalizations. Of the remaining injuries, one patient sustained a superficial stab wound to the abdomen, another sustained serious maxillofacial trauma, and a third person died from a thermal injury.

Thirteen patients had injuries involving multiple sites. Nine of these patients died while hospitalized. The remaining 27 patients had injuries involving a single site; of these, three died.

The presence of clinical or laboratory findings associated with hepatic insufficiency in this group of patients

TABLE 3. *Injury Characteristics*

Site	Total	Nonsurvivors (%)
Head	15	6 (40)
Thorax	7	4 (57)
Abdomen	9	6 (67)*
Pelvis/Ext	25	8 (32)
Multiple	13	9 (69)*
Single	27	3 (11)

* $p < 0.05$.

TABLE 4. *Presence of Hepatic Insufficiency*

Parameters of Hepatic Insufficiency†	Total	Nonsurvivors (%)
Ascites	19	9 (47)*
SGOT > 40 μ/L	13	6 (46)
Alk phos. > 125 μ/L	13	6 (46)
Ser bili. > 2.0 mg/dL	17	10 (60)*
Ser alb. ≤ 3.0 mg/dL	22	7 (32)
PT > Control	15	8 (53)*

* $p < 0.05$.

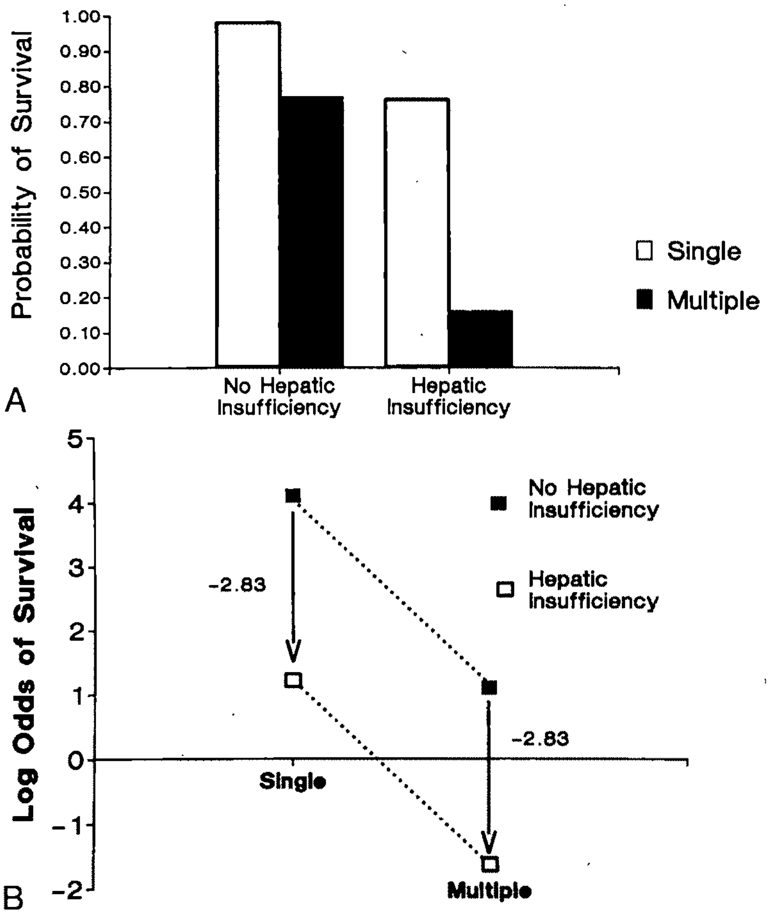
† As determined by clinical exam and laboratory data on admission. SGOT, serum glutamic oxaloacetic transaminase; Alk phos., alkaline phosphate; Ser bili., serum bilirubin; Ser alb., serum albumin; PT, alkaline phosphatase.

is outlined in Table 4. For comparison, the presence of these parameters in the 12 nonsurvivors is listed as well. The presence of ascites was confirmed by operative findings or radiologic evidence in 19 patients. Of these, nine died. Elevation of prothrombin time to more than 12.5 seconds was found in 15 patients, including eight nonsurvivors. Serum bilirubin in excess of 2 mg/dL was found in 17 patients on admission, of whom ten died (50%). The presence of any of these parameters was associated with significant increases ($p < 0.05$) in mortality. Elevations in SGOT and alkaline phosphatase and hypoalbuminemia were present in various patients, but did not significantly affect outcome.

Twenty-two patients had evidence of ascites, hyperbilirubinemia and/or elevated prothrombin time. This group's mortality rate was 50%, which was significantly greater ($p < 0.05$) than the predicted mortality rate of 12%. In the 18 patients without any abnormality in these parameters, only one death occurred, yielding a 6% mortality rate, which was not significantly different from predicted.

Loglinear analysis revealed that these parameters of hepatic insufficiency (ascites, hyperbilirubinemia, and elevated prothrombin time) and the presence of multiple injuries independently affected patient outcome. Both had a uniform negative effect on survival (Fig. 1).

Of the 12 patients who did not survive, three patients died of closed head injury; the remaining nine patients succumbed to multiple-system organ failure. In these nine patients, hepatic failure was either the inciting factor or played an integral role in the patient's demise. The demographics of this group are contained in Table 5.



FIGS. 1A and B. (A) Displays probability of survival of patients with single or multiple sites of injury as related to hepatic insufficiency. (B) Displays the uniform impact of hepatic insufficiency on log relative odds of survival when single or multiple sites of injury are involved.

Discussion

Hepatic cirrhosis invariably follows hepatocellular necrosis.[18] Cirrhosis, regardless of etiology, inhibits the liver's response to injury. The predominant histologic features are wide-spread fibrosis and nodule formation with loss of normal hepatic architecture. These changes are manifested clinically by hepatic failure and portal hypertension, the magnitude of which determines an individual patient's course and prognosis.

Adequate hepatic function is necessary in the physiologic response to surgery or traumatic injury. The liver performs a vital role in protein synthesis, detoxification, and immunologic response. In a patient subjected to surgical intervention or traumatic injury, any degree of hepatic insufficiency would diminish the liver's ability to carry out these vital metabolic functions. Thus, because of impaired cirrhotic reserve, a cirrhotic surgical or trauma patient would be at great risk for morbid complication or death during the recovery period.

The increased risk to the cirrhotic patient undergoing surgery has been well documented.[3-15,19-20] Essentially the basis of Child's criteria was to classify operative risk in cirrhotic patients undergoing portosystemic shunt surgery.[19] Child[20,21] showed that the degree of hepatic decompensation correlated with the rate of operative mortality in these patients. Furthermore other studies had shown that if therapeutic measures were taken to improve the cirrhotic patient's clinical status before operation and upgrade his Child's class, postoperative outcome after portosystemic shunting was improved.

In fact surgery of various types carries increased risk in the cirrhotic patient. In 1963 Lindenmuth and Eisenberg[15] studied 91 patients with varying degrees of cirrhosis. They reported an overall complication rate of 25% and a mortality rate of 8% after operative procedures, which ranged in magnitude from herniorrhaphy to major gastrointestinal surgery and included portosystemic shunting. A more recent review by Doeberneck et al.[5] in 1983 reported operative mortality rate as 19.6% and morbidity rate of the survivors as 47%. Interestingly 16 of the 20 patients who died underwent exploratory laparotomy and intra-abdominal surgery without portosystemic shunting. The mortality rate for this group alone was 35% while the operative mortality rate for the remainder of the patients undergoing herniorrhaphy, orthopedic repair, genitourinary surgery, or portosystemic shunting was 9%.

It has been appreciated that surgery not involving portosystemic shunting, but requiring laparotomy, poses a grave risk to the cirrhotic patient. Schwartz,[7] Cryer et al.,[8] and Arahna et al.[11] have studied cirrhotic patients undergoing biliary tract surgery. They reported mortality rates of 27%, 21%, and 24%, respectively. These rates are far in excess of the 1.7% reported morality rate for the noncirrhotic patient undergoing biliary tract surgery.[21] Furthermore Garrison and coworkers reviewed 100 consecutive patients with biopsy-proved cirrhosis undergoing various intra-abdominal operations.[6] Similar to the reviews previously cited,[7,8,11] the patients in this group who underwent surgery on their biliary tract had a mortality rate of 21%. In addition mortality rates for gastroduodenal surgery (35%), small bowel surgery (60%), colon resection (56%), and even open liver biopsy (20%), were exceedingly high as compared to rates in noncirrhotic patients. In 1986 Arahna et al.[4] reviewed their own experience with cirrhotic patients undergoing intra-abdominal surgery, exclusive of that involving the biliary tract or portosystemic shunting, and reported an overall operative mortality rate of 64%.

Despite these dismal figures, it is clear that certain cirrhotic patients undergo surgical intervention with only a moderate increase in risk. As alluded to before, those patients undergoing nonabdominal surgery fared reasonably well.[5,12,14] Furthermore, in all studies cited,[3-15] those pa-

TABLE 5. *Demographic Data on Nonsurvivors*

Age	Sex	TS	ISS	Mechanism	HD	Injury	OR	Cirr. Etiol.	Cause of Death
67	M	6	34	Fall	20	Multiple	Lap	ETOH	CHI, Sepsis
66	M	8	34	MVA	2	Multiple	Lap	ETOH	Coag, Sepsis, MSOF
68	M	14	20	MVA	7	Multiple	ORIF	ETOH	Hepatic failure, MSOF
53	M	15	26	MVA	11	Multiple	Lap	ETOH	Hepatic failure, MSOF
70	F	16	34	Explosion	6	Single	—	ETOH	Hepatic failure, MSOF
50	M	9	34	MVA	2	Multiple	ORIF	ETOH	CHI
76	F	16	9	Fall	30	Single	—	Crypt.	Hepatic failure, MSOF
46	M	4	34	MVA	7	Multiple	Lap	ETOH	Coag, Sepsis, MSOF
41	M	12	16	Fall	10	Single	—	ETOH	CHI, Pneumonia
64	M	14	14	Fall	25	Multiple	ORIF	ETOH	Hepatic failure, MSOF
72	F	16	14	MVA/PED	18	Multiple	ORIF	Crypt.	Hepatic failure, MSOF
57	F	15	22	MVA/PED	22	Multiple	Lap	ETOH	Hepatic failure, MSOF

HD, hospital days; Lap, laparotomy; ORIF, open reduction/internal fixation; CHI, closed head injury; Coag, Coagulopathy; MSOF, multiple system organ failure; MVA, motor vehicle accident; PED, pedestrian-motor vehicle accident; ETOH, ethanol; crypt, cryptogenic.

tients with only minimal evidence of impaired hepatic function had significantly lower morbidity and mortality rates than patients who had clinical and laboratory findings of hepatocellular failure (*i.e.*, ascites, encephalopathy, elevated serum bilirubin, elevated prothrombin times, and/or decreased serum albumin). In fact Sirineck and colleagues[3] have recently shown that the mortality rate can be significantly reduced by instituting perioperative therapeutic measures (previously used before portosystemic shunting) to control ascites, correct abnormal coagulation defects, and nutritionally replete the cirrhotic surgical patient.

Most important, the cirrhotic patient does not tolerate emergency surgery. When compared to elective procedures, cirrhotic patients of similar Child's class had as much as a threefold increase in mortality rate.[4,6] Arahna et al.[4] reported a mortality rate of 86% in patients with advanced cirrhosis who underwent emergency surgery. This is understandable because no effort can be made to improve the clinical status in a cirrhotic patient undergoing emergency surgery. The cirrhotic trauma victim characteristically resembles the cirrhotic undergoing emergency surgery. Like emergency surgery, traumatic injury and its treatment allows little time for optimizing the cirrhotic patient's hepatic functions and clinical condition. Therefore it is apparent that the cirrhotic trauma patient is at grave risk and has an overall poor prognosis as does the cirrhotic undergoing emergency surgery. Interestingly we could find no published reports pertaining to cirrhosis in trauma victims. Garrison's[6] series included four cirrhotic patients who underwent exploratory laparotomy for trauma, three of whom died, but did not deal with these cases specifically. The intention of our study was to clarify this situation and characterize this group of patients.

As with the cirrhotic surgical patient, the mortality rate among our patients was higher than expected. The 30% mortality rate was significantly higher than predicted in relation to the severity of the specific injuries as reflected by TRISS. The associated Z statistic of -6.92 quantitates this difference. On the other hand, the M("match") statistic quantifies the difference in the distribution of probability of survival (P_s) ranges in our study population and the Multiple Trauma Outcome Study (MTOS) norm. The M statistic of 0.86 showed that our patients were distributed over higher P_s ranges, indicating that as a group they were less severely injured than the MTOS population.

Several factors portended poor outcome in our group. Although the predominant mechanism of injury was falls, those patients involved in motor vehicle accidents (MVA) fared the worst. Because the severity of associated injuries was increased with MVAs as the mechanism of injury, this outcome would be expected.

Regarding site of injury, patients sustaining blunt abdominal trauma with hemoperitoneum or visceral injury, requiring laparotomy, incurred a significant increase in mortality (67%). This mirrored the surgical cirrhotic patient in which the highest mortality rates were associated with laparotomy and intra-abdominal surgery. The presence of multiple injuries increased total injury severity and, as expected, was the injury characteristic associated with the highest increase in mortality rate (69%). On the other hand there were only three deaths (11%) in the group of 27 patients with injuries involving a single site.

Child's criteria could not be used to classify these patients. Nutritional status and response to therapy were unobtainable. Furthermore mental status changes on admission could not be solely attributed to hepatic etiology. However the evidence of hepatic insufficiency, as determined by the presence of ascites and/or elevated prothrombin time, correlated with outcome in these patients, as it has in patients undergoing operative intervention. Multivariate analysis revealed that the cirrhotic trauma victim presenting with ascites, hyperbilirubinemia, or elevation in prothrombin time exhibited a uniformly lower rate of survival independent of injury characteristics. In fact, of the seven patients presenting with all three abnormalities, none survived.

Certainly a study population of this size limits the information that can be yielded. A multicenter study, using urban populations, will be necessary to fully evaluate and characterize the effects of cirrhosis on patients sustaining traumatic injuries. Until such information can be compiled, the data embodied in this review confirms the similarity of the cirrhotic trauma patient to the cirrhotic patient undergoing emergency surgery. As with surgery patients, cirrhosis in the trauma victim is associated with a significant increase in mortality rate. Admission markers of poor outcome include one or more of the following: ascites, hyperbilirubinemia, elevated prothrombin time, multiple injuries, or blunt abdominal trauma requiring laparotomy. Finally the presence of hepatic insufficiency on admission increases mortality rate regardless of the injury sustained.

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Distal Splenorenal Shunt *Versus* Endoscopic Sclerotherapy in the Prevention of Variceal Rebleeding

First Stage of a Randomized, Controlled Trial

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In 1984 we started a prospective controlled trial comparing endoscopic sclerotherapy (ES) with the distal splenorenal shunt (DSRS) in the elective treatment of variceal hemorrhage in cirrhotic patients. The study population included 40 patients with cirrhosis and portal hypertension referred to our department from October 1984 to March 1988. These patients were drawn from a pool of 173 patients who underwent either elective surgery or endoscopic sclerotherapy during this time. Patients were assigned to one of the two groups according to a random-number table: 20 to DSRS and 20 to ES. During the postoperative period, no DSRS patient died, while one ES patient died of uncontrolled hemorrhage. One DSRS patient had mild recurrent variceal hemorrhage despite an angiographically patent DSRS. Four ES patients suffered at least one episode of gastrointestinal bleeding: two from varices and two from esophageal ulcerations. Five ES patients developed transitory dysphagia. Long-term follow-up was complete in all patients. Two-year survival rates for shunt (95%) and ES (90%) groups were similar. One DSRS patient rebled from duodenal ulcer, while three ES patients had recurrent bleeding from esophagogastric sources (two from varices and one from hypertensive gastropathy). One DSRS and two ES patients have evolved a mild chronic encephalopathy; four DSRS and two ES patients suffered at least one episode of acute encephalopathy. Two ES patients had esophageal stenoses, which were successfully dilated. Preliminary data from this trial seem to indicate that DSRS, in a subgroup of patients with good liver function and a correct portal-azygos disconnection, more effectively prevents variceal rebleeding than ES. However no significant difference in the survival of the two treatment groups was noted.

THE SELECTIVE DISTAL splenorenal shunt (DSRS) proposed by Warren et al.[1] in 1967 appeared to be the best procedure available for surgical decompression of patients with portal hypertension.[2-4] It seemed to combine the advantages of the definitive treatment of varices, typical of totally diverting shunts, without harmful loss of hepatopetal portal flow. This resulted in a better quality of life, as reported in several studies comparing the clinical results of selective and nonselective shunts.[3-9]

It has been shown that endoscopic sclerotherapy (ES) protects against variceal rebleeding when compared to a medical regimen[10-12] and improves long-term survival,[13] resulting in a possible alternative to shunt surgery.

To evaluate the efficacy of these treatments, we started a prospective controlled trial in 1984 comparing the efficacy of ES and DSRS in the prevention of variceal rebleeding in cirrhotic patients.[17]

Our study is similar to three recently published randomized controlled trials.[14-16]

Methods

The study population comprised 40 patients with cirrhosis and portal hypertension referred to our department from October 1984 to March 1988. These patients were drawn from a pool of 173 patients who underwent either elective surgery or endoscopic sclerotherapy because of portal hypertension during this time.

The criteria for inclusion into the study were (1) liver cirrhosis confirmed by biopsy in all patients; (2) endoscopic documentation of variceal hemorrhage (actively bleeding varix or nonbleeding varices without other lesions) requiring at least one unit of blood transfusion; (3) arrest of acute variceal hemorrhage either spontaneously

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or by use of intravenous vasopressin and/or somatostatin and/or balloon tamponade and/or hemostatic sessions of ES; (4) patient age of less than 70 years; (5) good or moderate liver function (Child's A and B class);[18] (6) patency of the splanchnic venous system and hepatopetal portal flow (according to Nordlinger's classification);[19] (7) eligible for either shunt or ES; (8) absence of life-threatening diseases (*i.e.*, tumors); and (9) willingness to return for regular sclerosis and follow-up. Patients bleeding from gastric varices were excluded. Figure 1 shows the reasons for the exclusion of 133 patients. Randomization was done when the patient was stabilized, no more than 24 hours before treatment. Patients were assigned to one of the two groups according to a random-number table. Informed written consent was obtained from all patients before their inclusion in the study. No patient refused the assigned treatment. Variceal rebleeding within 2 years of first treatment was considered the primary measure of patient outcome. The sample requirements to show a decrease in variceal rebleeding from 43% to 7% are about 20 patients for each group, applying standard power (90%), type I error ($p < 0.05$) and a two-tailed t test.[20]

Preoperative Evaluation

A complete medical history was obtained in each patient with particular attention to previous episodes of gastrointestinal bleeding and evidence of either primary or posthemorrhagic hepatic failure (jaundice, ascites, or edema). Physical examination concentrated on the assessment of the nutritional state and the presence of hepatosplenomegaly, jaundice, ascites, and edema. Routine laboratory tests were performed to evaluate liver function (Table 1). An overall assessment of the severity of liver disease (hepatic score index) was made at the time of patient inclusion in the study to complete Child's classification and adequately compare the two groups of patients.[3] A score from 1 to 3 according to the level of severity was assigned to each clinical and laboratory parameter. The total of the scores, the maximum of which is 27, was called the hepatic score sum. It is often impossible to compare different hepatic score sums because of missed parameters in some patients. Thus the hepatic score index was expressed as the ratio of the hepatic score sum to the highest possible hepatic score sum. Serum alfafeto-protein and ultrasonography were routinely obtained to screen the presence of hepatic neoplasm. The etiology of cirrhosis was determined from clinical history, serum markers of viral hepatitis and liver biopsy. The presence of esophageal varices was assessed through endoscopic examination. Criteria used for classifying the endoscopic findings were based on the General Rules for Recording Endoscopic Findings on Esophageal Varices compiled by the Japanese Research Society for Portal Hypertension.[21]

Cerebral function was assessed through a complete neurologic examination, taking into account the mental state, asterixis, electroencephalographic findings (EEG), and the trail making test.[21,23] All parameters were assessed

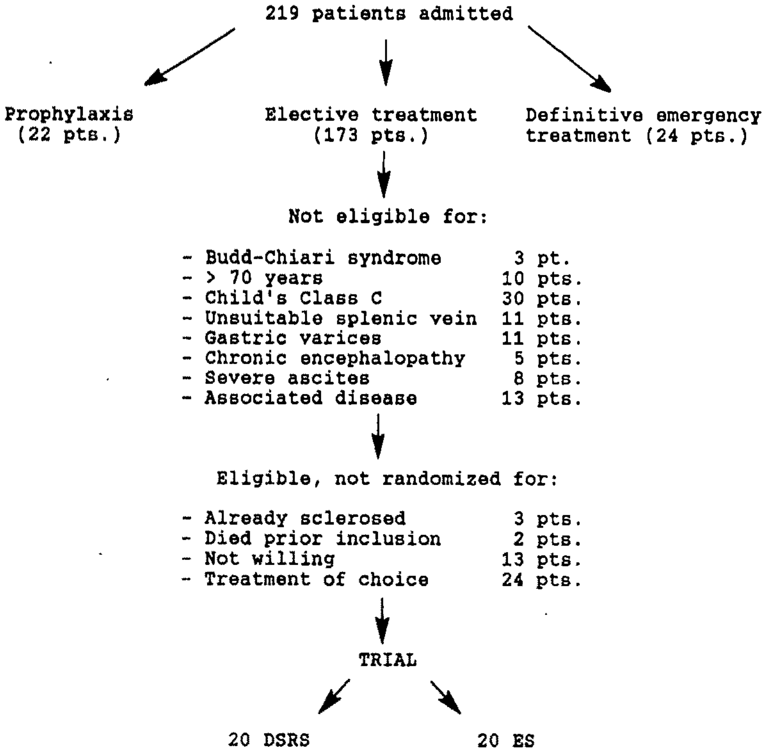
219 patients admitted
Prophylaxis (22 pts.)
Elective treatment (173 pts.)
Definitive emergency treatment (24 pts.)
Not eligible for:
- Budd-Chiari syndrome 3 pt.
- > 70 years 10 pts.
- Child's Class C 30 pts.
- Unsuitable splenic vein 11 pts.
- Gastric varices 11 pts.
- Chronic encephalopathy 5 pts.
- Severe ascites 8 pts.
- Associated disease 13 pts.
Eligible, not randomized for:
- Already sclerosed 3 pts.
- Died prior inclusion 2 pts.
- Not willing 13 pts.
- Treatment of choice 24 pts.
TRIAL
20 DSRS
20 ES

FIG. 1. Reasons for exclusion.

TABLE 1. *Characteristics of Patients*

Characteristic	DSRS (n = 20)	ES (n = 20)
Age (years)	46.9 ± 10.3	51.2 ± 8.2
Sex M/F	11/9	16/4
Etiology*		
Alcoholic	2	13
Nonalcoholic	18	7
Child's class		
A	8	7
B	12	13
Hepatic score	0.52 ± 0.05	0.58 ± 0.08
Prothrombin time (%)		
>80	2	5
80–50	15	11
<50	3	4
Bilirubin (mg/dL)		
<1.2	13	9
1.2–3	7	8
>3	0	3
Albumin (gr/dL)		
>3	18	18
3–2.5	2	2
<2.5	0	0
Portal perfusion		
Degree I	36%	27%
II	53%	40%
III	12%	33%
N. of previous bleeding	2.3 ± 1.7	1.9 ± 1.0
N. of blood unit	3.1 ± 2.3	2.2 ± 2.1
Interval between bleeding and treatment (months)	3.2 ± 2.3	3.1 ± 2.4
N. of previous encephalopathy episodes	5	5
Easily controlled preoperative ascites	2	3

* Alcoholic *versus* nonalcoholic: p = 0.0031.

using the 0 to 4 rating system proposed by Conn.[24] The "Cancelling A's" test was also used[25] and rated with the same method. Each parameter was arbitrarily weighted in proportion to its importance. Mental state was assigned a factor of 4, asterixis and EEG a factor of 1, and each of the others a factor of 0.5. An overall score for hepatic encephalopathy (HE) was calculated from the sum of the values for each of the five parameters.[4] We called HE "acute" if it was precipitated by gastrointestinal bleeding, heavy drinking, pharmacologic or dietary imbalances, of brief duration and easily controlled with elimination of precipitating cause. We called HE chronic if it was spontaneous, of long duration, and more difficult to manage. Naturally preoperative HE was excluded in all patients.

A visceral angiogram was obtained by selective catheterization of celiac axis and superior mesenteric artery. The degree of hepatic perfusion was evaluated according to Nordlinger's criteria.[19] The rate of contrast (sodium and meglumine ioxaglate, Hexabrix 320—Byk Gulden, Milan, Italy) infusion was 6 mL/seconds × 10 seconds.

Operative Management

All shunts were performed by a single experienced surgical team.[26] DSRS was constructed according to the technique described by Warren[27] (15 cases). In five cases a splenopancreatic disconnection[28] was performed as a technical addition to DSRS, offering the optimum surgical therapy to each patient.

Endoscopic variceal sclerosis was conducted by two endoscopists with extensive experience in this field.[29] All patients were given 5 to 10 mg diazepam premedication. ES was performed using an Olympus GIF IT (Lorenzatto, Torino, Italy) flexible endoscope or an electronic Welch Allyn videoendoscope (Coresea, Milan, Italy). At each session 10 to 50 mL of polidocanol (0.5% to 1%) (Athoxysclerol, Creusller) and 0.5% methylene blue were injected using a flexible injection needle in the area 5 to 7 cm above the esophagogastric junction. Methylene blue allowed visual confirmation of intravariceal and paravariceal injections.

Postoperative Evaluation

In the evaluation of the hospital mortality rate and early complications, we defined the first 30 days after the initial treatment as the postoperative period. In the ES group, the events that occurred during the interval between the first session and eradication were also recorded and evaluated.

In the postoperative period, esophageal endoscopy was performed in each patient. A visceral angiography was performed on the 10th average postoperative day only in patients having DSRS. Shunt patency was verified in venous phase of angiograms in the DSRS group. In the ES group, the number of further sessions depended on the findings obtained at endoscopy performed 1 week after the first sclerosis session. As soon as the eradication was achieved, the patient was included in the follow-up program. The remaining ES patients underwent further sclerosis sessions if they were free of complications such as mucosal ulcerations, symptomatic stricture, severe esophagitis, fever, and pneumonia. In the presence of complications, an upper endoscopy was performed at intervals of seven to ten days and further ES sessions were considered only when complications were resolved. During the follow-up period, DSRS patients were checked the first, third, and sixth month after discharge and then at least twice yearly, on an outpatient basis. Follow-up endoscopy was scheduled 4 to 6 weeks after the last session and then at 6-month intervals, unless recurrent hemorrhage occurred.

At each visit, liver function was evaluated after a complete medical examination and laboratory tests. Longitudinal assessment of liver function was quantified using an arbitrary score calculated on the basis of several standard laboratory tests. Synthesis activity (albumin and prothrombin time determinations), excretion (bilirubin and alkaline phosphatase levels) and the presence of hepatocellular necrosis (serum glutamic-oxaloacetic transaminase determinations) were quantified by the same method previously described for the preoperative assessment of global functional hepatic reserve.[3] This index was obtained yearly after treatment and compared each time with preoperative values. It was only used for the longitudinal assessment of liver function and termed longitudinal hepatic score index. Child's classification and the preoperative hepatic score index were not suitable to follow-up because some parameters could not be assessed over a long period of time.

The assessment of the neurologic status was performed using the above-mentioned criteria. An EEG was obtained at least once a year. A return to drinking was based on patient's statements, our own assessment, and information from relatives. Continued drinking was defined as daily consumption in excess of 1 L of wine and/or spirits. All patients were on a 10-meq sodium and protein-balanced diet (1 g protein/Kg body weight) and undergoing lactulose prophylactic treatment: the initial dose was 60 g/day in three separate doses and adjusted thereafter to induce at least one bowel movement per day.

Definitions

Eradication was defined as absence of varices or presence of F1 white varices. Rebleeding was defined as hemorrhage due to esophagogastric varices and/or congestive gastropathy that required at least one unit blood transfusion and was designated as being from varices if supported by endoscopic findings. The ideal treatment of variceal rebleeding was emergency sclerotherapy. Chronic rebleeding from congestive gastropathy was treated with beta-blocking therapy.[30] Rebleeding due to peptic ulcer was recorded separately.

The risk of hospitalization for HE was defined by taking the number of late hospital admissions due to episodes of HE and dividing it by the total number of patients evaluated in the follow-up period.

Death, whatever the cause, was considered failure of therapy in both groups. Failure of shunt was defined as shunt thrombosis on follow-up angiographic evaluation. Sclerotherapy failure was defined as a change to surgery due to recurrent hemorrhage or severe complications that prevented further ES. This decision was taken by the endoscopists and surgeon and was not based on a specific number or degree of severity of the recurrent bleeding episodes.

Data Management and Statistical Analysis

Initial evaluation and subsequent follow-up data were collected on databases (Excel, Microsoft Corp., Cologno, Monzese, Italy) for computer input (Epson PC AX computer, Seiko Epson Corporation) and subsequent analysis (Microstat, Ecosoft Inc., Indianapolis, IN). Survival and therapy failures were analyzed by the Kaplan–Meier method and were compared by the log-rank test.[31] Comparison between groups was made by chi square test for proportions and Student's t test for the means.

Results

In the ES group, varices were completely eradicated in 19 patients (95%): one patient died before eradication. The number of injection sessions were 3.1 ± 1.1 (95% CI from 2.6 to 3.6 months), occurring over 4.8 ± 3.7 months (95% CI from 3.2 to 6.4 months) and the mean amount of polydocanol required for eradication was 89.4 ± 43.6 mL (95% CI from 70 to 108.7 mL).

During the postoperative period, no DSRS patient died, while one ES patient died of uncontrolled hemorrhage after the first sclerosis session. One DSRS patient had mild recurrent variceal hemorrhage controlled by conservative therapy, despite an angiographically patent shunt. Four ES patients suffered at least one episode of gastrointestinal bleeding. Two were from varices requiring emergency variceal sclerotherapy and two from esophageal ulcerations, which were managed conservatively. No patient had episodes of hepatic encephalopathy. Five ES patients developed transitory dysphagia due to esophageal ulcerations. One ES patient suffered pleural space effusion.

The mean follow-up in the DSRS group was 29.2 ± 11.4 months (95% CI from 24.2 to 34.1 months) and the mean follow-up in the ES group was 23.8 ± 14.8 months (95% CI from 23.8 to 30.3 months). Two-year survival rates for shunt (95%) and ES (90%) groups were similar (Fig. 2). One DSRS patient died of intestinal obstruction, one of liver cancer and one of heart failure. One ES patient died of hepatic failure and one of unknown causes. Failure of therapy was at that moment equal to the death rate: no patient had shunt thrombosis or changed treatment. In the ES group, varices reformed in 5 of 19 eradicated patients (26%) after 8.6 ± 7.4 months (95% CI from 2 to 15.3 months). They were successfully re-eradicated. No DSRS patient had variceal rebleeding (one DSRS patient rebled from duodenal ulcer), while two ES patients had recurrent hemorrhage from varices and one from hypertensive gastropathy. The global percentage of patients who rebled was 5% and 35%, respectively ($p = 0.04$). Actuarial curves of patients free from esophagogastric rebleeding, for the two groups, confirmed the efficacy of DSRS (Fig. 3). One DSRS and two ES patients developed mild chronic

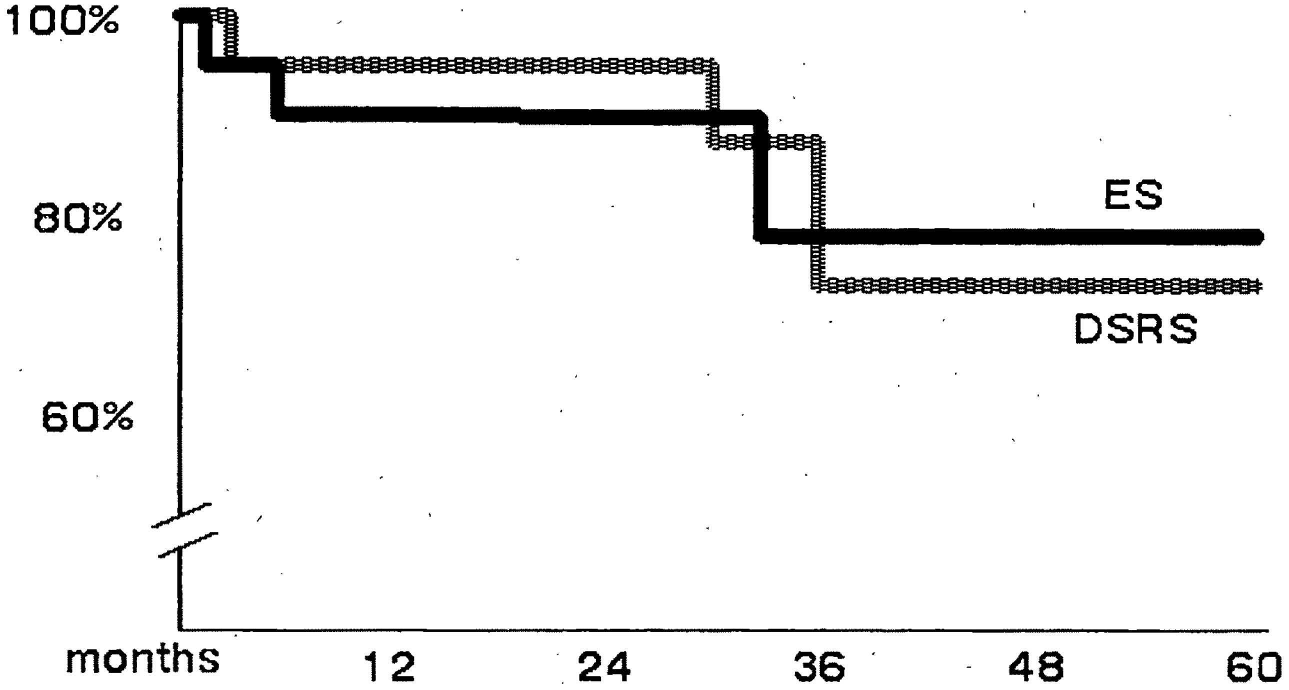

FIG. 2. Actuarial survival curves for distal splenorenal shunt (DSRS) and endoscopic sclerotherapy (ES). The vertical axis indicates the survival rate. No significant difference was noted using the log-rank test.

encephalopathy. Four DSRS and 2 ES patients suffered at least 1 episode of acute encephalopathy (p was not significant): 2 (1 DSRS and 1 ES) due to pharmacologic imbalance, 2 (1 DSRS and 1 ES) due to heavy drinking, 1 DSRS due to dietary abuse and 1 DSRS due to severe hyperglycemia. The results of trail-making test (TMT), cancelling A's test and electroencephalography (EEG) confirmed the similar outcome in the two groups of pa-

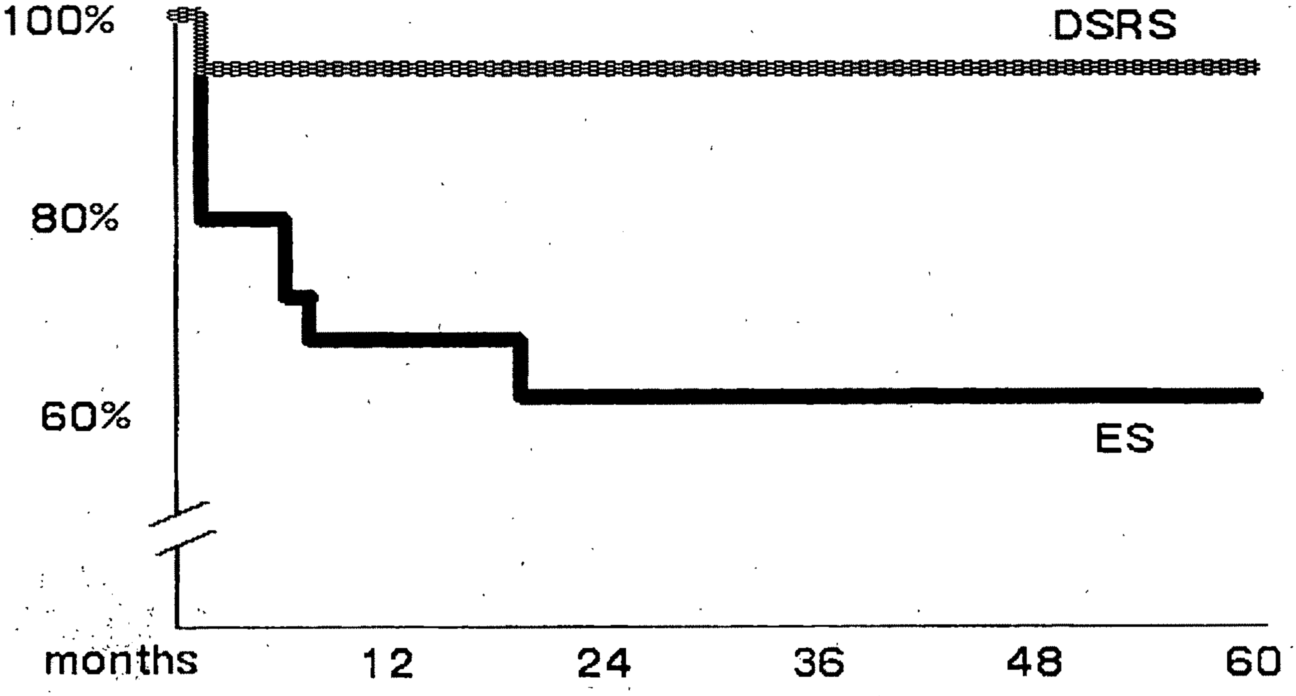

FIG. 3. Actuarial curves of patients free from gastroesophageal rebleeding for distal splenorenal shunt (DSRS) and endoscopic sclerotherapy (ES). The vertical axis indicates the rate of patients free of gastroesophageal rebleeding. The DSRS group has significantly prevented gastroesophageal rebleeding compared to ES ($p < 0.05$) using the log-rank test.

TABLE 2. *Comparison of the Results of TMT, Cancelling A's Test, and EEG*

Period	Preoperative	Long-Term Follow-up
TMT (sec.)		
DSRS	50.8 ± 20.5	52.1 ± 21.3
ES	61.9 ± 17.9	60.2 ± 24.5
A's test*		
DSRS	4.4 ± 3.1	3.5 ± 3.3
ES	5.8 ± 4.5	5.2 ± 3.5
EEG (% abnormal)†		
DSRS	15%	20%
ES	15%	21%

* Refers to the number of A's the patients have omitted to cancel in the test.

† p value not significant for all comparisons.

tients on yearly examination (Table 2). The risk of hospitalization for HE was similar: 0.25 ± 0.9 and 0.21 ± 0.7 after DSRS and ES, respectively (p was not significant). One DSRS patient (5%) and four ES patients (21%) went back to drinking (p was not significant). Two ES patients had esophageal stenosis that were successfully dilated. Ascites developed in two DSRS patients (5%) and in ten ES patients (53%; $p = 0.01$). Longitudinal data of liver function tests were available on 18 ES and 19 DSRS patients at 1 year. ES did not cause changes in hepatic function (from 0.53 ± 0.14 to 0.53 ± 0.14), whereas after the DSRS procedure there was significant impairment in function at 1 year (from 0.54 ± 0.10 to 0.61 ± 0.11; $p = 0.012$).

Discussion

The pattern of a randomized controlled trial (RCT), comparing surgical treatment with a conservative therapy like ES, is often a complicated process requiring a choice of end-point patient selection criteria, treatment schedules, and methods of patient evaluation. Three RCTs,[14–16] in addition to our study, have been published comparing DSRS to ES. They show different approaches to these issues.

It is true that survival is the primary end-point in prospective studies. In two studies[14,16] the definition of major end-point was not specified (survival, prevention of recurrent bleeding, and maintenance of hepatic function) and no statistical method for determining trial size was used. The study of Terés et al.[15] was designed to observe an increase in survival. However the expected increase seems to be too optimistic. On the basis of the available data,[2,5,10–13] the sample requirements to show a realistic increase in survival at 5 years of the 10% is about 470 patients per group, applying standard power (80%), type I error ($p < 0.05$) and a two-tailed t test.[20]

Because gastroesophageal rebleeding was the most life-threatening complication in ES, we wanted to verify if DSRS was more effective in the prevention of rebleeding than ES and evaluate if this improvement affected survival. We limited the necessary recruitment to 20 patients per group, so the trial needed only one surgical team. This is a general problem in surgical multicenter trials, as the surgeon's skill is a major factor in the outcome of the patients, especially when a technically complex operation like DSRS is used.[32] Our trial was undertaken after the team had acquired experience with 80 selective shunts, to ensure a fairly good standardization of the surgical approach and intraoperative and postoperative treatment.[5] However the patient's inclusion has not been stopped at 20 cases for each group. In fact the random choice in our trial does not prevent a problem reported in Table 1, which shows a statistical difference in etiology between the two groups. Although our experience did not attribute a prognostic role to etiology,[3,33] some studies indicated a more favorable prognosis for survival in nonalcoholics compared to alcoholics.[34,35] We then decided to increase the number of patients to be recruited either to eliminate the difference or carry out a subgroup analysis.

This study also differs from the other RCTs[14–16] because of the trial design, particularly if we consider the criteria of inclusion and exclusion and the number of patients seen and rejected. Figure 1 shows the criteria of exclusion used in our trial. Some choice in the study design caused an increase in the number of patients rejected. In fact 219 patients were admitted to our department: 22 patients were considered to have had no previous variceal bleeding and had prophylactic treatment, and 24 patients had active variceal bleeding that was treated on an emergency basis. They were excluded because they received definitive treatment (portocaval shunt, esophageal transection) or were lost or died after hemostatic session of sclerotherapy. Ninety-one of 173 patients evaluated were not eligible for inclusion in the study. Finally 13 patients were unwilling to return for regular sclerosis and 24 patients were not included because they had not undergone preoperative angiography or were sent to us with previous indications to DSRS or sclerosis. Our selection criteria excluded 77% of patients with previous variceal bleeding. This value was similar to that reported in another study (83%).[14] Other studies[15,16] excluded fewer patients (44% and 62%, respectively). However Terés et al.[15] had additional exclusions after randomization (16%) due to technical reasons.

The results of these trials[14–17] confirm previous results showing that DSRS is more effective in preventing variceal rebleeding than ES (Table 3). Gastroesophageal rebleeding after DSRS can be caused by either gastroduodenal lesions or esophageal varices. The most common cause of variceal rebleeding is shunt thrombosis, but hemorrhage can also occur when the shunt is patent because of renal vein hypertension.[36]

TABLE 3. *Two-Year Survival and Rebleeding Rate in Randomized Controlled Trials Comparing DSRS with ES*

	Warren[14]	Terés[15]	Rikkers[16]	Our Data
Two-year survival rate after DSRS	59%	71%	65%	95%
Two-year survival rate after ES	84%	68%	61%	90%
Child's C patients	43%	0	33%	0
Interval between bleeding and treatment (days)	>3–5	10–15	NR	90*
Rebleeding rate after DSRS	3%†	14%†	19%†	5%†
Rebleeding rate after ES	53%†	37%†	57%†	35%†
Variceal eradication rate	NR	46%	63%	95%
Failure to salvage rebleeders	17%	33%	47%	14%
Shunt for ES failure	31%	6%	7%	0
Global mortality rate due to rebleeding	3%	14%	27%	5%
Global mortality rate due to other causes	13%	16%	13%	10%

NR, not reported.
* Mean value.
† $p < 0.05$.

The problem of rebleeding in the ES group is complex and is related to factors such as the number of patients with eradicated varices, the time interval required for eradication, the incidence of sclerosis-induced mucosal ulcerations of the esophageal wall, the variceal relapses after eradication, and the incidence of hypertensive gastropathy.[37] Our incidence of rebleeding (35%) is similar to that reported by Teres et al.,[15] but lower compared to other studies.[14,16] The importance of the different techniques to explain these differences is not clear.[38,39] It is obvious that a more aggressive technique of ES, characterized by endoscopic examinations at shorter intervals or by more ES sessions, could be more effective in preventing variceal rebleeding. However this potential benefit could be cancelled by a higher risk of rebleeding from sclerosis-induced mucosal ulcerations. Our sclerotherapy regimen did not follow a rigid time protocol. Because of the unpredictability of individual responses, it is unlikely that an optimal schedule can be suitable to all patients. The different rate of rebleeding in these RCTs can not be explained only by the failure in varices eradication. The different interval between hemorrhage and beginning of the surgical or endoscopic treatment can be an important factor. Different treatment intervals have been shown to affect the incidence of variceal rebleeding.[40] Finally it is a common experience that early rebleeding occurs frequently in Child's C patients[14] and the number of Child's patients differed in all these RCTs.

Hypertensive or congestive gastropathy is a serious complication due to raised portal pressure. DSRS reduces the gastric blood flow and prevents this complication. In the ES group two patients (one had also a variceal rebleeding) had five episodes of bleeding due to gastropathy. The evident temporal relationship between the use of beta-blockers and hemorrhage control supports its therapeutic efficacy. This concomitant therapy in the ES group was used only after digestive hemorrhage. Patients with endoscopic findings of congestive gastropathy, without hemorrhage, were not prophylactically treated with beta-blocker agents.

The 2-year survival rate ranged from 59% to 95% in DSRS and from 61% to 90% in the ES group (Table 3). Why are there these great differences?

The different incidence in these studies of two prognostic factors (Child's class C patients and the interval between hemorrhage and treatment) can explain these results.[41] However a more important factor is present in the ES group: the fate of the patient after variceal rebleeding (Table 3). The fact that some studies[15,16] do not have a good therapeutic option in the case of ES failure can influence these results. The best survival rate reported in Warren's study[14] seems to be due to the large number of ES patients submitted to shunt surgery (10 of 36 patients) with a low operative mortality rate (10%). This advantage was not shown in the other studies.[15,16] This can be explained by the fact that shunt surgery compromises liver function, thus death due to liver failure becomes the major cause of death instead of hemorrhage.[33] In fact, in our study, DSRS patients had significantly decreased liver function 1 year after shunt surgery, when compared to the preoperative values (0.54 ± 0.10 *versus* 0.61 ± 0.11). The mean difference was 0.07, with a 95% confidence interval from −0.001 to 0.141. We do not know the actual clinical significance of this difference, even if statistically significant. The ES patients, on the other hand, did not show any impairment in liver function. This might be explained by the fact that patients in the ES group with alcoholic cirrhosis eliminated alcohol abuse, resulting in improved liver function.

The main complication for the shunted patient was chronic HE that little affected ES patients. In the four RCTs the incidence of HE was higher in the DSRS group than in the ES group. This trend became significant in Teres' study,[15] probably due to the modified technique used, which did not associate portal-azygos disconnection with splenorenal shunt. In fact the entity of collaterals after DSRS seems to be an important factor influencing the incidence of HE.[42–45] In Rikkers'[16] and Warren's[14] studies chronic HE was probably attributed to the hepatic failure, and that was due to the fact that both Child's C patients[14,16] and total shunts[16] were taken in consideration. In our study,[17] the low rate of chronic HE in the DSRS group could be due to the recruitment of patients with good liver function and a shorter follow-up period than in other studies. The results of the psychometric tests and EEG confirmed the similar outcomes in the two groups of patients at 1-year follow-up evaluation.

ES was more often complicated by ascites than was DSRS. However ascites almost always responded to standard diuretic therapy. The complication rate of ES was low. In our experience,[17] only two patients had esophageal stenosis. This was the only complication that affected the quality of life in the ES group. Similar rates were shown in two RCTs[15,16] (10%), while Warren et al.[14] had no complications after ES.

In conclusion DSRS seems to be more effective than ES for preventing gastroesophageal rebleeding. However this improvement was not followed by an increase in patient survival. Indeed early survival was significantly improved by ES only when shunt surgery was available for uncontrolled bleeding.[46] Whether shunt rescue is an artefact of analysis or a valid phenomenon is not known. Further investigations are necessary to confirm if ES might be the first stage of a therapeutic regimen completed by definitive therapy, *i.e.*, surgery.

Which is the best treatment? In some patients the choice is easy because it is mandatory. ES is indicated for patients with unsuitable splenic vein or high risk of HE. DSRS is indicated for patients with gastric variceal bleeding or recurrent hemorrhage, despite sclerotherapy. In other cases the decision whether to shunt or to perform ES should be made only after having carefully studied all characteristics of every patient. To achieve good results, it is important that every time we make our decision we take patient compliance into account. The patients should be informed that shunt surgery is more traumatic but more definitive for bleeding and that sclerotherapy has a minimal impact on hepatic functional reserve but is less effective in preventing rebleeding and demands a rigorous follow-up.

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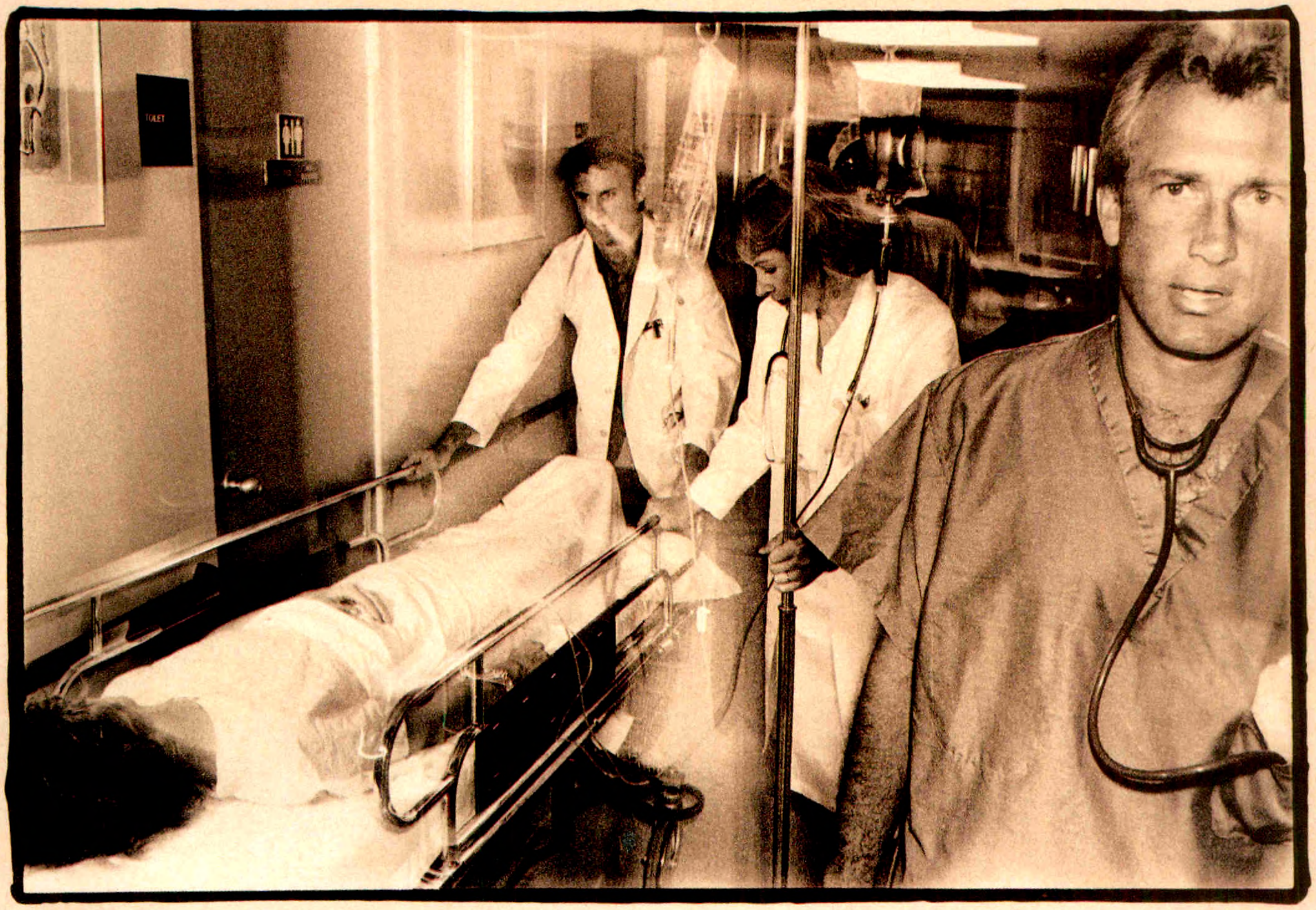

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INDICATIONS AND USAGE
UNASYN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.
Skin and Skin Structure Infections caused by beta-lactamase producing strains of *Staphylococcus aureus*, *Escherichia coli*,* *Klebsiella* spp.* (including *K. pneumoniae**), *Proteus mirabilis*,* *Bacteroides fragilis*,* *Enterobacter* spp.,* and *Acinetobacter calcoaceticus*.*
Intra-Abdominal Infections caused by beta-lactamase producing strains of *Escherichia coli*, *Klebsiella* spp. (including *K. pneumoniae**), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*
Gynecological Infections caused by beta-lactamase producing strains of *Escherichia coli*,* and *Bacteroides* spp.* (including *B. fragilis**).
*Efficacy for this organism in this organ system was studied in fewer than 10 infections.
While UNASYN* (ampicillin sodium/sulbactam sodium) is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.

CONTRAINDICATIONS
The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS
SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.
SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS
General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.
Drug Interactions: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.
Drug/Laboratory Test Interactions: Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with UNASYN.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.
Pregnancy
Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)
Labor and Delivery: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.
Nursing Mothers: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.
Pediatric Use: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.

ADVERSE REACTIONS
UNASYN is generally well tolerated. The following adverse reactions have been reported.
Local Adverse Reactions
Pain at IM injection site—16% Pain at IV injection site—3%
Thrombophlebitis—3%
Systemic Adverse Reactions
The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.
Additional systemic reactions reported in less than 1% of the patients were itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.
Adverse Laboratory Changes
Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:
Hepatic: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.
Hematologic: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.
Blood Chemistry: Decreased serum albumin and total proteins.
Renal: Increased BUN and creatinine.
Urinalysis: Presence of RBC's and hyaline casts in urine.
The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.
Gastrointestinal: Gastritis, stomatitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.
Hypersensitivity Reactions: Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin (see WARNINGS).
Hematologic: In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

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(ampicillin sodium/sulbactam sodium)

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INDICATIONS AND USAGE
UNASYN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.
Skin and Skin Structure Infections caused by beta-lactamase producing strains of *Staphylococcus aureus*, *Escherichia coli*,* *Klebsiella* spp.* (including *K. pneumoniae**), *Proteus mirabilis*,* *Bacteroides fragilis*,* *Enterobacter* spp.,* and *Acinetobacter calcoaceticus*.*
Intra-Abdominal Infections caused by beta-lactamase producing strains of *Escherichia coli*, *Klebsiella* spp. (including *K. pneumoniae**), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*
Gynecological Infections caused by beta-lactamase producing strains of *Escherichia coli*,* and *Bacteroides* spp.* (including *B. fragilis**).
*Efficacy for this organism in this organ system was studied in fewer than 10 infections.
While UNASYN* (ampicillin sodium/sulbactam sodium) is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.
CONTRAINDICATIONS
The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.
WARNINGS
SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.
SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.
PRECAUTIONS
General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.
Drug Interactions: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.
Drug/Laboratory Test Interactions: Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with UNASYN.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.
Pregnancy
Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)
Labor and Delivery: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.
Nursing Mothers: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.
Pediatric Use: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.
ADVERSE REACTIONS
UNASYN is generally well tolerated. The following adverse reactions have been reported.
Local Adverse Reactions
Pain at IM injection site—16% Pain at IV injection site—3%
Thrombophlebitis—3%
Systemic Adverse Reactions
The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.
Additional systemic reactions reported in less than 1% of the patients were: itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.
Adverse Laboratory Changes
Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:
Hepatic: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.
Hematologic: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.
Blood Chemistry: Decreased serum albumin and total proteins.
Renal: Increased BUN and creatinine.
Urinalysis: Presence of RBC's and hyaline casts in urine.
The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.
Gastrointestinal: Gastritis, stomatitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.
Hypersensitivity Reactions: Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin (see WARNINGS).
Hematologic: In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

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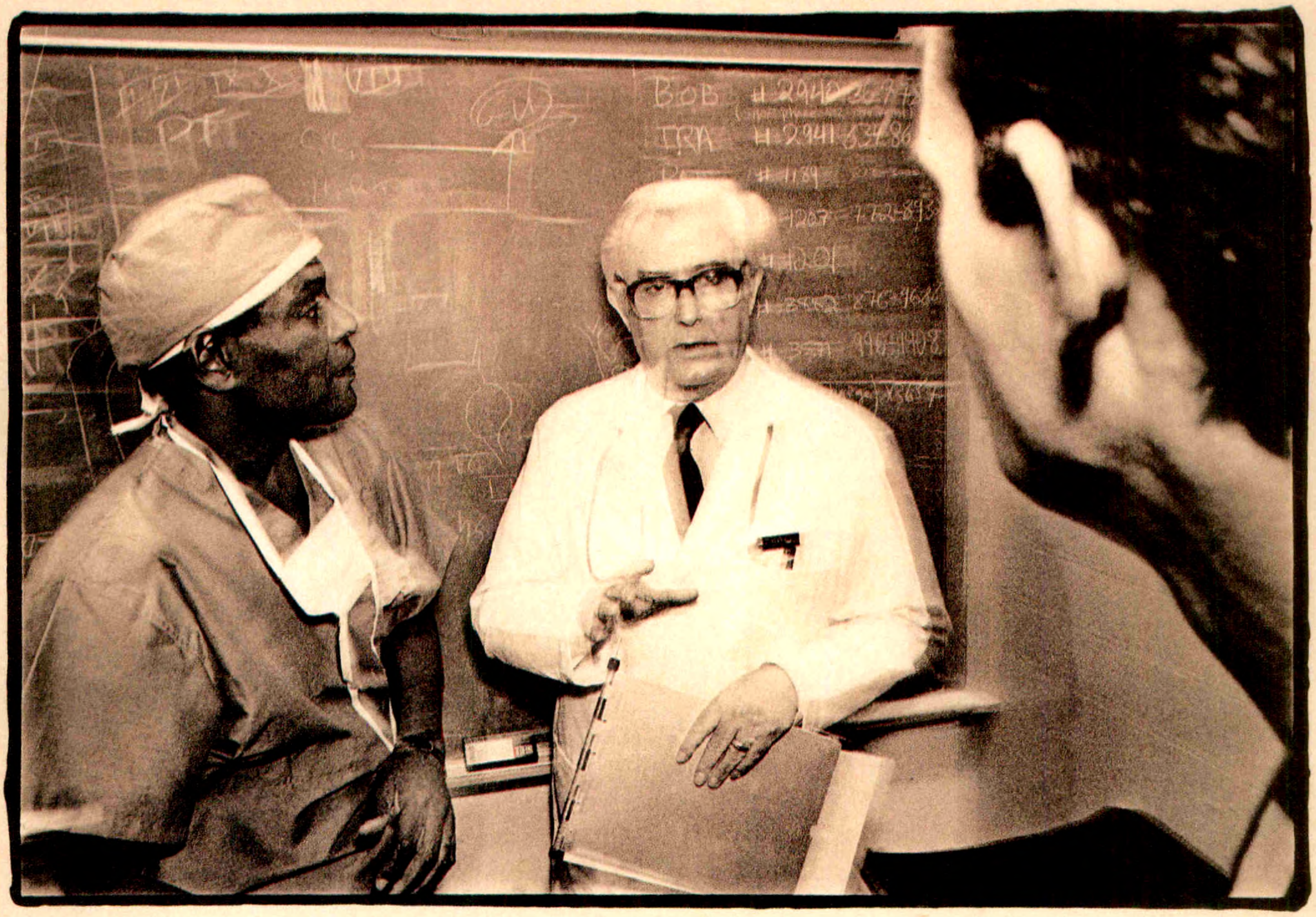

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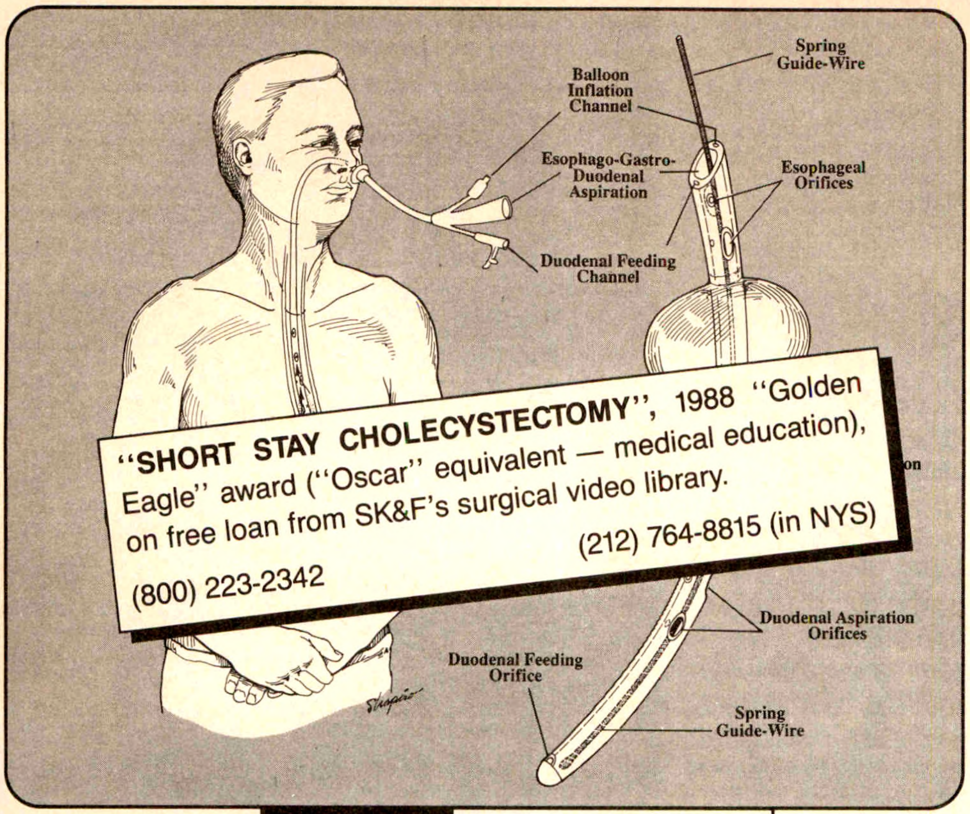

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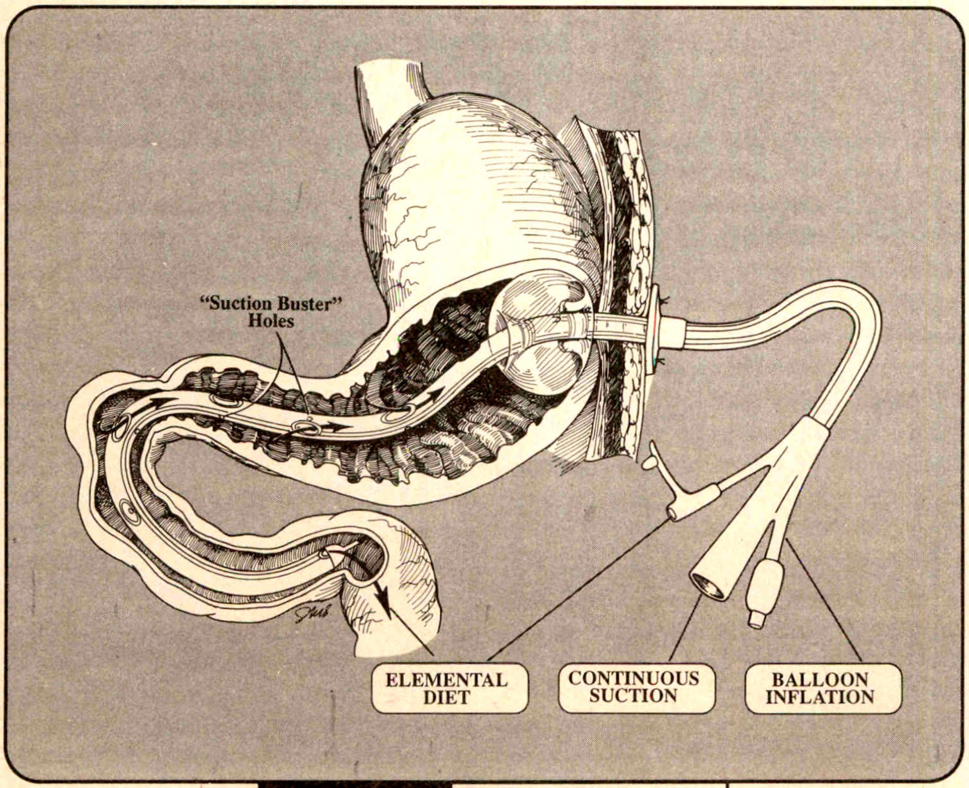

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CASE # 24 **AGE:** 55 **SEX:** FEMALE

DIAGNOSIS: CECAL CARCINOMA

SYMPTOMS: ANEMIA (Hg 6 gm/dl)

OPERATION: RIGHT HEMICOLECTOMY & GASTROSTOMY

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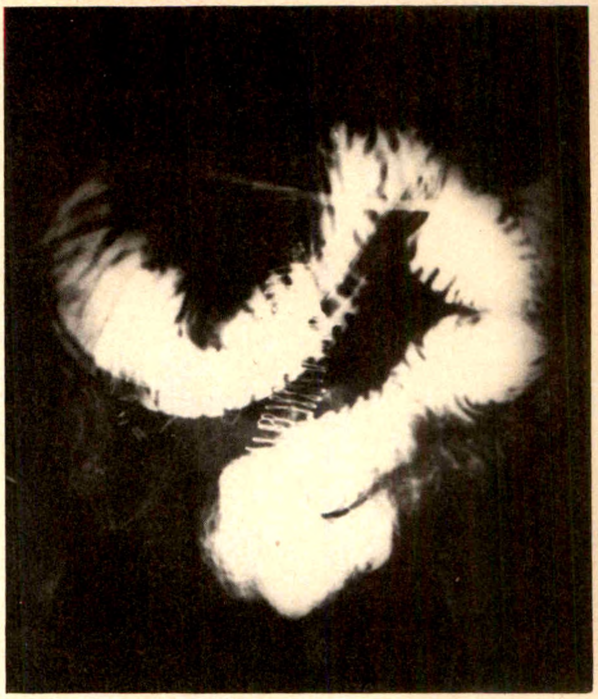
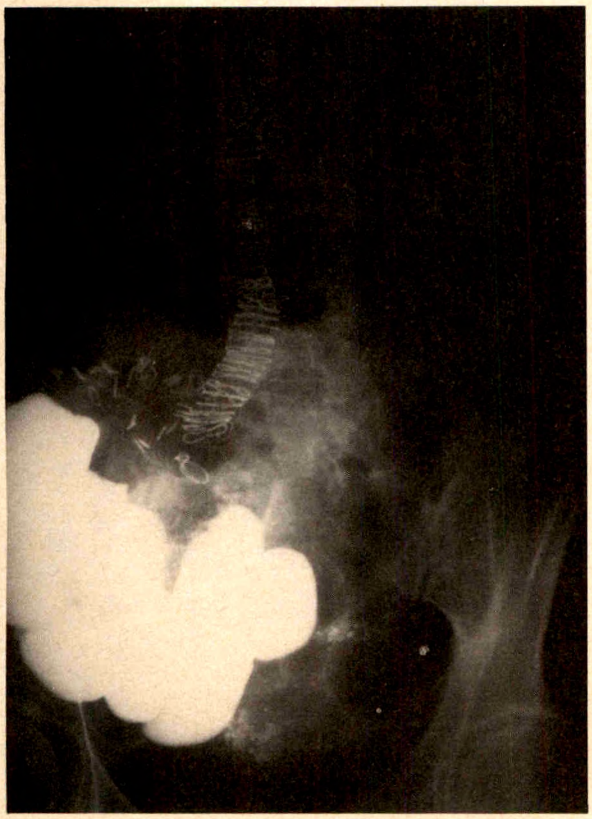
Barium feeding 5 hours postop documented adequate motility. The deliberate excess was totally removed. No contrast (i.e.: excess feeding) escaped efficient aspiration within the proximal duodenum, to reflux into the stomach. (Figure A) Serial motility study showed barium had traversed the anastomosis and colon, and already was exiting in a spontaneous bowel movement by 21 hours postop. (Figure C)

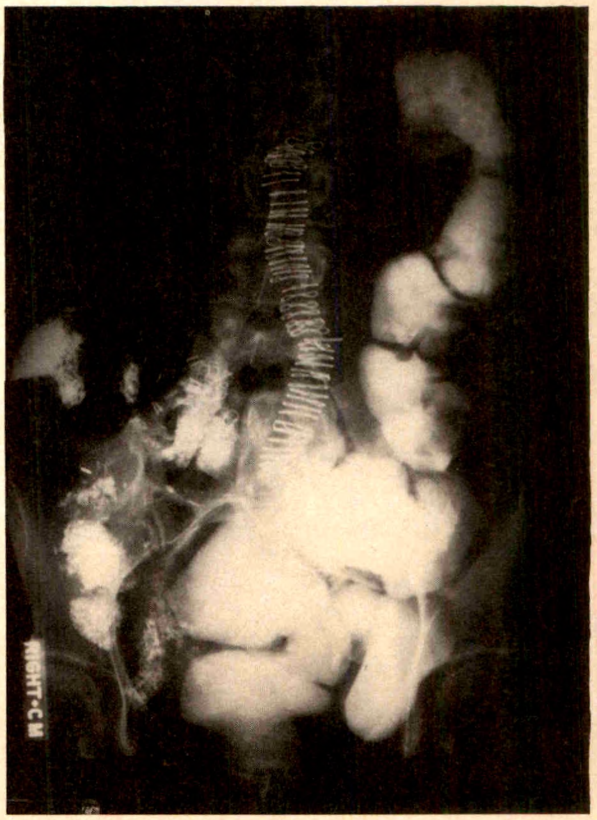
She received 300 ml/hr of Vivonex TEN (Norwich Eaton Pharm), absorbed 5,000 kcal the initial 20 hours, and then tolerated a general diet. She was the 4th patient discharged uneventfully 24 hours after bowel resection and reanastomosis.



A. Study @ 5 minutes (5 hours postop).
Note efficient removal of all excess barium, with none reaching the stomach.



B. Motility @ 4 hours (9 hours postop).
All barium is within the ileum.



C. Motility @ 16 hours (21 hours postop).
Barium is exiting in a spontaneous bowel movement.

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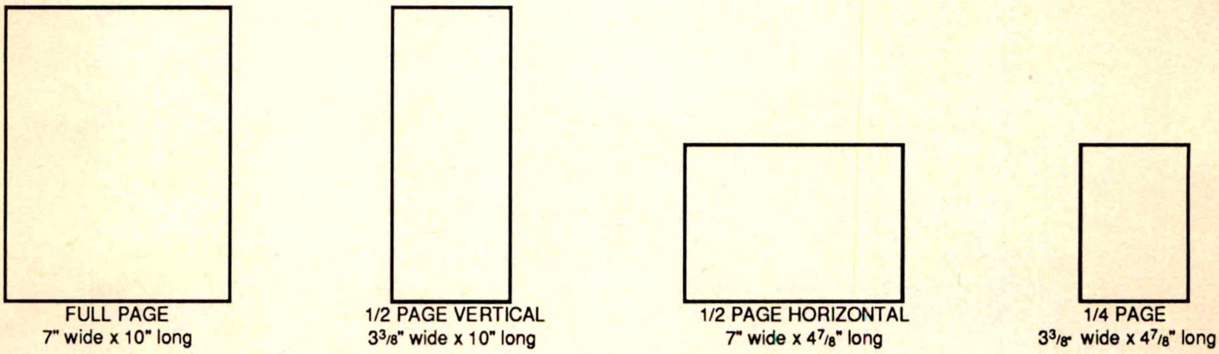

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Pre- or Postoperative Radiotherapy in Rectal and Rectosigmoid Carcinoma

Report from a Randomized Multicenter Trial

LARS PÅHLMAN, M.D., PH.D.,* and BENGT GLIMELIUS, M.D., PH.D.†

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Between October 1980 and December 1985, 471 patients with a resectable rectal carcinoma entered a randomized multicenter trial for comparison of pre- and postoperative irradiation. Two hundred thirty-six patients were allocated to receive high-dose fractionated preoperative irradiation (total dosage, 25.5 Gy in five to seven days) and 235 patients to receive postoperative irradiation to a very high dosage level with conventional fractionation (60 Gy in a total 8 weeks). The postoperative treatment was delivered only to a high-risk group of patients (Astler-Coller stages B_2, C_1, and C_2). The preoperative irradiation was well tolerated, with no immediate irradiation-related complications and no increased postoperative mortality (3%, 7 of 217 patients, compared to 5%, 10 of 215 patients in the postoperatively irradiated group). More patients in the preoperative irradiation group had perineal wound sepsis after abdominoperineal resection and this prolonged the stay in hospital after surgery. In 50% of the patients the postoperative treatment could not be commenced until more than 6 weeks after surgery. The postoperative treatment was not as well tolerated as the preoperative one. The local recurrence rate was statistically significantly lower after preoperative than after postoperative radiotherapy (12% *versus* 21%; $p = 0.02$). In both groups more patients developed a local recurrence if the bowel was perforated at surgery or if the resection line was microscopically close to the tumor. To date, with a minimum follow-up of 3 years and a mean follow-up of 6 years, there is no difference in survival rates between the two groups.

LOCAL RECURRENCES AFTER curative surgery for rectal carcinoma are common, although the rates reported in the literature have varied from less than 10% to as much as 65%.[1-6] The skill of the surgeon,[5] patient selection, and/or different follow-up routines have been discussed as reasons for this variability. With perioperative radiotherapy, provided the dosage level has been sufficiently high (> 40 Gy in 3 to 4 weeks, or a comparable dosage level with other fractionation schedules), the local recurrence rate has been substantially reduced.[7-9] One major question is whether an additional treatment should preferably be given before or after operation, or both. With postoperative radiotherapy, groups of patients found to be at low risk of local recurrence can be excluded from therapy, whereas at present this is not possible when preoperative therapy is used.

In 1980 a trial for comparison of preoperative radiotherapy at a high dosage level with a postoperative radiotherapy regimen to an even higher dose given only to high-risk groups of patients was initiated. The primary aim of the trial was to investigate whether the local recurrence rate differs between the two treatment modalities. A secondary aim was to compare the survival. An interim report on the trial was published shortly before the end of the inclusion of the patients.[10] This second report will focus on the acute effects of the treatment, the local recurrence rate, and the survival after a minimum follow-up of 3 years (mean, 6 years).

Materials and Methods

Patients

Between October 1980 and December 1985 all patients with a tumor in the rectum or rectosigmoid (18 to 20 cm or less from the anal verge as measured at rigid sigmoidoscopy) were recruited to the trial from a defined area of Sweden. Patients with primarily operable tumors in whom an anterior resection or an abdominoperineal resection was considered, were randomly allocated either to a preoperative group, in which all patients were to have radiotherapy, or to a postoperative group in which the radiotherapy was to be given only to high-risk groups of patients (Fig. 1).

Supported by grants from the Swedish Cancer Society (Project No. 1783-B89-08XC).

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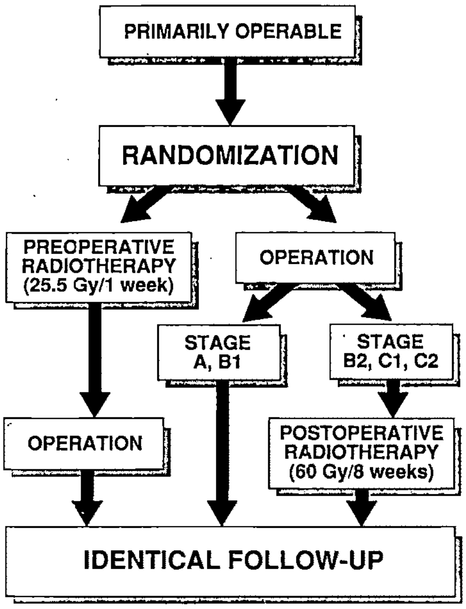

FIG. 1. Treatment protocol for rectal carcinoma.

Exclusion criteria included

(1) locally inextirpable tumors, *i.e.*, tumors fixed to the pelvic wall or genitourinary organs (excluding the vagina) and large bulky tumors that were not really mobile;
(2) previous radiotherapy to the pelvis;
(3) high age and/or poor condition (no upper age limit was used);
(4) advanced generalized disease; and
(5) other malignant generalized disease.

Of a total 471 patients from whom informed consent was obtained, 236 patients were randomly allocated to the preoperative group and 235 to the postoperative group. The age and sex distributions are given in Table 1.

During the same time period, a primary adenocarcinoma of the rectum was diagnosed in 123 additional patients. Fifty-nine of these patients had a tumor that was considered locally inextirpable and 64 had an extirpable tumor. Those patients were not included in the trial because of a high age or poor condition (29 patients), advanced distant metastases (9 patients), previous radiotherapy to the pelvic region (6 patients), other malignant disease (9 patients), refusal of treatment (8 patients), and inconclusive preoperative biopsy (7 patients).

TABLE 1. *Age and Sex Distributions of the Initially Included 471 Patients*

	Preoperative Group			Postoperative Group		
		Age			Age	
	n	Median	Range (yrs)	n	Median	Range (yrs)
Men	134	71	(42–84)	138	70	(40–83)
Women	102	72	(44–87)	97	69	(39–87)

Surgery and Histopathology

Standard surgical procedures were used and the choice of operative procedure rested on the surgeon. Locally radical surgery included a bowel with a radically resected tumor with free margins at histopathologic examination. If the bowel was damaged during surgery but a free margin was observed histopathologically, the operation was considered radical. The operative specimen was classified according to a modification of Dukes' staging system:

A = tumor limited to the mucosa and submucosa; negative lymph nodes;
B_1 = tumor extension into but not through the muscularis propria; negative lymph nodes;
B_2 = tumor extension through the muscularis propria; negative lymph nodes;
C_1 = tumor extension into but not through the muscularis propria; positive lymph nodes; and
C_2 = Tumor extension through the muscularis propria; positive lymph nodes.

This is a slightly modified version of what has been referred to as the Astler-Coller modification of Dukes' staging system.[11]

Irradiation

The irradiation technique has been described previously.[12] Briefly, the target volume included the whole dorsal part of the pelvic cavity from the anus up to L4. The irradiation was given with one mid-dorsal and two angled dorsal portals with the patient in a prone position (Fig. 2). The relative biologic effect of the irradiation on

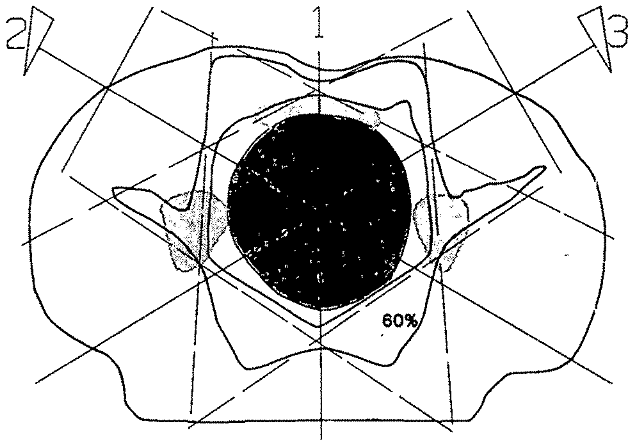

FIG. 2. Plan of irradiation. Transverse section through S3 with the patient in a prone position. The target area is closely encompassed by the 95% isodose curve.

normal cells was calculated according to the CRE (cumulative radiation effect) concept,[13] with corrections for late effects on normal tissue (corrected CRE) as suggested by Turesson.[14]

Preoperative irradiation. All patients allocated to this treatment group should receive a total tumor dose of 25.5 Gy in five fractions of 5.1 Gy daily over five to seven days. The corrected CRE values for five days and seven days were 15.4 and 14.9, respectively, corresponding to 47 to 49 Gy given with fractions of 2 Gy daily (10 Gy/week). The patients were operated on within 1 week after radiotherapy.

Postoperative irradiation. Patients with a tumor in stage A or B_1 as evaluated at the postoperative histopathologic examination did not receive any radiation, even though they were randomly allocated to the postoperative group. According to the intended schedule, the postoperative radiotherapy should ideally have been started within 4 to 6 weeks after surgery. Irradiation was delivered in a dose of 2 Gy daily, five days per week for 4 weeks. After an interval of 10 to 14 days, further radiation was given for a period of 2 weeks to a total dose of 60 Gy. The target volume was reduced during the last 10 Gy. This dose corresponds to a CRE value of 17.0 to 17.2, the variation depending on the length of the interval.

Follow-up Routines

The patients were followed clinically every third month during the first postoperative year, every fourth month in the second year, and twice a year up to at least 5 years. Since the fifth year, the patients have been followed yearly. Computed tomography (CT) of the pelvic region was performed at least once, 6 to 9 months after surgery. Several patients have been examined repeatedly.[15] Supplementary CT investigations were carried out if there was any clinical suspicion of recurrence. In the event of any clinical or roentgenologic suspicion of local recurrence, *e.g.*, if a mass was observed at CT, a fine-needle and/or true-cut biopsy directed to the region in question was performed. Only patients with a morphologically proved recurrent cancer within the pelvic cavity were recorded as having local recurrence. According to the protocol, a morphologic diagnosis should be the objective.

Statistics

Patients were randomly allocated to the two groups according to a self-adjusting randomization plan.[16] The material was stratified according to oncological department, sex, and tumor level (low tumors 0 to 10 cm, high tumors 11 to 20 cm). A total 441 patients had to be included to detect a difference in the local recurrence rate of 10% (from 10% to 20%), with a significance level of 0.05 and a probability of a successful test of 0.9. The power calculation was done with 10% drop-outs. Differences in local recurrence rate and survival were evaluated by the log-rank test.[17] In the survival calculations all patients were included, whereas only patients with locally radically resected tumors were included when differences in local recurrence rates were evaluated. Postoperative mortality was calculated among all patients who underwent a resection.

Results

Treatment

In the preoperative group all patients but one received the intended radiation, and in all but 14 the treatment was given according to schedule, *i.e.*, during five to seven days. In these 14 patients the treatment was prolonged for one to three days, mainly because of holidays. The preoperative radiotherapy was extremely well tolerated without any radiation-related adverse effects during the treatment period. Surgery was performed as scheduled within 1 week (seven days) after the end of the irradiation in all but 21 patients; in these patients it was performed between 8 to 22 days, except in two patients who had no surgery (Table 2). In 209 (89%) of the patients in the preoperative group the operation was locally curative (Table 2).

In the postoperative group, 204 (87%) patients had a resection that was locally curative (Table 2). Of these 137 had a tumor in local stage B_2, C_1, or C_2 and therefore should have been referred to postoperative irradiation. Radiotherapy was started, however, in only 115 patients (84%). The other 22 patients did not receive radiotherapy for the following reasons: postoperative death (9 patients), prolonged postoperative recovery (8 patients), advanced distant metastases (4 patients), and treatment refusal (1 patient). None of the patients in stage A and B_1 received radiotherapy.

Among the 115 patients who were given radiotherapy after operation, the length of time from surgery to radia-

TABLE 2. *Outcome in the Two Groups*

	n
Preoperative group	236
Refused treatment	1
Patients irradiated	235
Refused surgery	1
Wrong preoperative histopathological diagnosis	1
No surgery because of poor condition	1
No resection because of liver metastases	12
Locally inextirpable at surgery	3
Locally nonradical surgery	8
Locally curative surgery	209
Postoperative group	235
Wrong preoperative histopathological diagnosis	6
No resection because of liver metastases	10
Locally inextirpable at surgery	7
Locally nonradical surgery	11
Locally curative surgery	204

TABLE 3. *Histopathologic Stage and Surgical Procedure in the Two Groups*

	Preoperative Group			Postoperative Group		
Local Stage	APR	AR	Total	APR	AR	Total
A	13 (1)	2 (1)	15 (2)	8	5	13
B_1	31 (2)	21 (1)	52 (3)	26 (4)	18 (3)	54 (7)
B_2	45 (6)	26 (3)	71 (9)	40 (10)	26 (7)	66 (17)
C_1	4	2	6	9 (2)	4 (1)	13 (3)
C_2	42 (10)	23 (2)	65 (12)	35 (8)	23 (8)	58 (16)
Locally nonradical	5 (1)	3 (2)	8 (3)	8 (3)	3 (1)	11 (4)
No resection			19			19
Total	140 (20)	77 (9)	236 (29)	136 (27)	79 (20)	235 (47)

Figures denote numbers of patients and figures in parentheses denote number of local recurrences.

APR, abdominoperineal resection; AR, anterior resection.

tion was 6 weeks or less (≤ 42 days) in 62 patients (54%), between 7 and 8 weeks (43 to 56 days) in 26 patients (23%), and more than 8 weeks (range, 56 to 95 days) in 27 patients (23%). In the majority of patients in whom radiotherapy was not started within 6 weeks, the reason for this was prolonged postoperative recovery (fatigue, nonhealed perineal wound). In some patients practical reasons such as not wanting to start therapy immediately before a big holiday or in the middle of a vacation also contributed. The tolerance to the postoperative radiotherapy was not as good as to the preoperative treatment. In nine patients the treatment was interrupted prematurely (4 to 36 Gy), the reason being fatigue in 3 patients, infectious complications in 4, a cerebrovascular lesion in 1, and a synchronous generalized renal carcinoma in 1 patient. Most of the patients had mild to moderate symptoms such as diarrhea, fatigue, nausea, skin reactions, and urinary tract disorders, particularly during the end of the first radiation period (see also Påhlman et al.[10]). Only in nine patients could the treatment be completed without any adverse effects.

Histopathology and Type of Surgery

There was no difference between the two groups with respect to the surgical procedure or histopathologic stage (Table 3). Of 209 patients with locally radical surgery in the preoperative group, 17 had distant metastases. Among the 204 patients with locally radical surgery in the postoperative group this figure was 15.

Complications of Surgery

Seven of the 209 patients with locally curative surgery in the preoperative group died after operation (3%). In the postoperative group, this proportion was 9 of 204 (4%). Based on all resected patients, *i.e.*, including those with a locally nonradical resection, the postoperative mortality rate was 3% in the preoperative group (7 of 217 patients) and 5% in the postoperative group (10 of 215 patients). Postoperative complications (Table 4) were equally distributed between the two groups, with one exception—that perineal wound sepsis after abdominoperineal resection occurred more often in the preoperative than in the postoperative group (33%, 45 of 135 patients *vs.* 18%, 23 of 128 patients; $p < 0.01$). This infection was treated with simple drainage and left open for secondary healing, and in all but three patients (two patients in the preoperative group and one patient in the postoperative group) the wound healed within 3 months. As seen in Table 5, the increased number of infected perineal wounds among preoperatively treated patients who underwent an abdominoperineal resection also affected the length of hospital stay because the longer stay among patients who received preoperative therapy was restricted to the group of patients who had this form of surgery.

TABLE 4. *Complications in Connection with Surgery**

Complication	Preoperative Group (n = 217)	Postoperative Group (n = 215)
Postoperative mortality		
Heart failure	3	5
Anastomotic dehiscence	2	1
Infectious complication	1	1
Ileus		2
Respiratory insufficiency	1	
Hematemesis		1
Perineal wound sepsis	45	23
Anastomotic dehiscence	14	13
Ileus-subileus	10	6
Postoperative fever	10	6
Abdominal wound sepsis	5	4
Abdominal wound rupture	7	4
Intra-abdominal abscesses or septicaemia	3	4
Thromboembolic disturbances	3	2
Stomal necrosis	4	4
Cardiovascular complications	2	3
Surgical mishaps	4	6
Pneumonia	—	1
Hematemesis	—	1

* Locally nonradical resections included.

TABLE 5. *Length of Stay After the Operation at the Department of Surgery, in Days*

	Preoperative Group				Postoperative Group				
	Range	Median	Mean	SD	Range	Median	Mean	SD	p Value
APR	9–146	28	38	25.3	9–79	25	28	14.6	$p < 0.001$
AR	7–100	17	23	18.9	7–100	16	22	19.1	$p > 0.05$
Total	7–146	25	33	23.6	7–100	20	26	16.6	$p < 0.01$

APR, abdominoperineal resection. AR, anterior resection.

Local Recurrence Rate

Statistically significantly more patients in the postoperative than in the preoperative group developed local recurrence (21%, 43 of 204 patient, *vs.* 12%, 26 of 209 patients, $p = 0.02$; Fig. 3, Table 6). This difference was noted in Astler-Coller stages B_2, C_1, and C_2. In stages A and B_1 the number of recurrences was small in both groups. Because of the small number of patients followed for more than 5 years (53 in the preoperative group and 45 in the postoperative group) an analysis of the differences in the local recurrence rate was performed on the findings at 5 years. The accumulated probability of developing a local recurrence at this time was 14.3% in the preoperative group and 26.8% in the postoperative group. The difference in local recurrence rate at 5 years was 12.5%, with a 95% confidence interval of 5% to 20%. Among patients in whom the bowel was perforated at surgery or in whom the resection line was close to the tumor microscopically, a local recurrence occurred significantly more often both in the preoperative ($p < 0.01$) and in the postoperative group ($p < 0.05$) than among those in whom the surgery was more definitely locally radical (Table 6). There was no difference between the two groups regarding the length of time between surgery and the development of a local recurrence (Fig. 3). Local recurrence developed in 3 of 17 patients with distant metastases in the preoperative group and in 2 of 15 in the postoperative group. Three of eight patients with locally nonradical surgery in the preoperative group displayed local recurrence, and 4 of 11 in the postoperative group. All patients with locally nonradical surgery in whom local recurrence did not develop died of cancer (nine patients) or intercurrent disease (three patients) within 18 months (median, 8 months) after surgery.

Distant Metastases and Survival

As seen in Figure 4, there was no difference between the two groups concerning the length of time that elapsed from surgery to the occurrence of a distant metastasis. So far there is no difference in overall survival between the two groups as calculated on the total material, or in cancer-specific survival estimated on the basis of patients operated on for total cure (Figs. 5 and 6).

Discussion

When discussing radiotherapy as an adjuvant to surgery, it is essential to remember that the minimum dose level required to kill micrometastases with a probability exceeding 90% is about 45 Gy in 4 weeks or a comparable dose level (CRE about 14.0) with other fractionation schedules.[18] With this figure in mind, influence on the

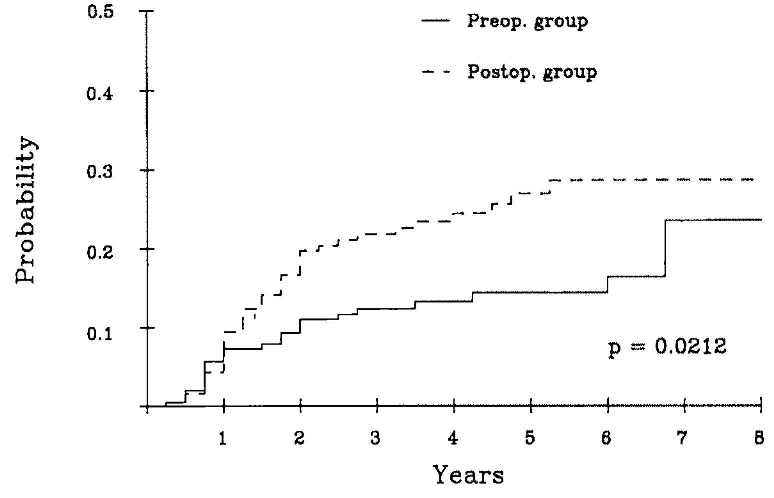

FIG. 3. Local recurrence rate after locally curative surgery in the two treatment groups.

TABLE 6. *Local Recurrences in Relation to the Findings at Histopathology and the Radicality of the Operation*

Group	Locally Satisfactory Surgery	Perforated Bowel	Histopathologically Close to Resection Line	Total
Preoperative				
A	11 (2)	4	—	15 (2)
B_1	45 (1)	6 (2)	1	52 (3)
B_2	57 (6)	8 (2)	6 (1)	71 (9)
C_1	6	—	—	6
C_2	47 (6)	10 (4)	8 (2)	65 (12)
Total	166 (15)	28 (8)	15 (3)	209 (26)
Postoperative				
A	9	4	—	13
B_1	47 (5)	7 (2)	—	54 (7)
B_2	52 (13)	12 (2)	2 (2)	66 (17)
C_1	11 (1)	2 (2)	—	13 (3)
C_2	38 (9)	17 (6)	3 (1)	58 (16)
Total	157 (28)	42 (12)	5 (3)	204 (43)

Figures denote number of patients (local recurrences).

local recurrence rate should not be expected in trials in which low dosage levels are used, and this has in fact been found to be the case.[19–23] In trials with higher dosage levels, a reduced local recurrence rate has been noted. In the EORTC trial preoperative irradiation to a comparably high dose level (CRE 13.0) reduced the local recurrence rate significantly.[7] An even larger reduction was achieved in the Stockholm trial,[8] in which a dose similar to our own (25 Gy in 1 week) was administered. In a Danish trial, in which a dose of 50 Gy in 5 weeks (CRE 15.2) delivered postoperatively was compared with surgery alone, no significant reduction in the local recurrence rate was found, except possibly in Dukes' B cases.[24] A slight reduction in the local recurrence rate was also observed in a GITSG study in which radiotherapy was given after operation to about 45 to 50 Gy in 4 to 5 weeks.[9] In that trial an even better effect was noted when radiotherapy was combined with chemotherapy.

Taken together results from trials using a surgery-alone arm as control indicate that preoperative irradiation at comparable, or even lower dosage levels, is more efficient in reducing the local recurrence rate than postoperative irradiation. This conclusion was strongly supported by the results of the present trial. Further in this trial we have used an unconventional preoperative treatment designed to be easy to deliver and to be a tempting alternative both for the patient and surgeon. On the other hand the treatment used in the postoperative group was designed to be the most satisfactory treatment that could be given as adjuvant therapy to patients with rectal tumors. In no other trial has such a high dosage level been used. In light of this it is interesting that a significantly lower local recur-

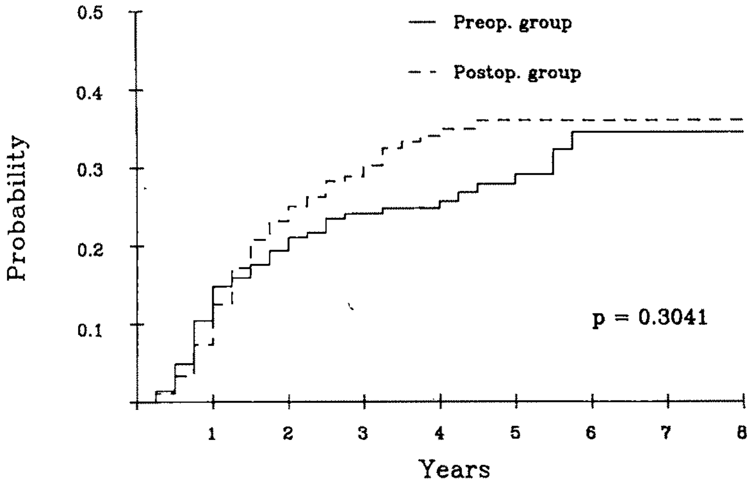

FIG. 4. Probability of development of distant metastasis after curative surgery in the two groups.

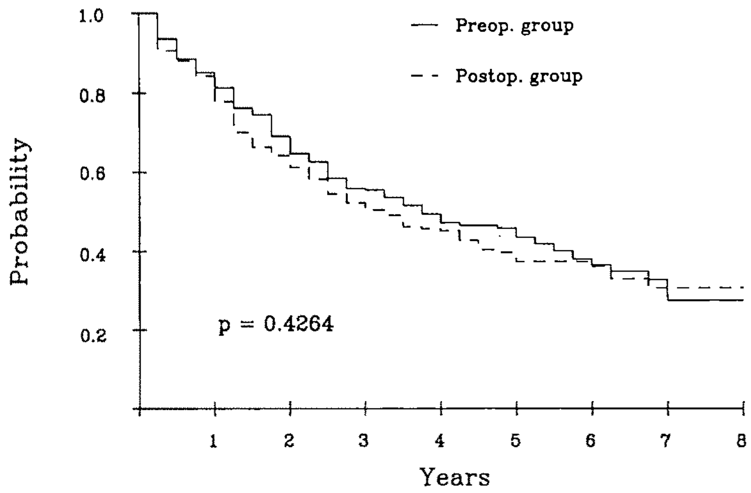

FIG. 5. Overall survival regardless of cause of death in the two groups.

rence rate was noted after the semi-optimal preoperative treatment than after the probably optimal postoperative treatment. The results support the idea that higher dosages are necessary to kill micrometastases in surgically disturbed tissue than in nondisturbed tissue.[18,25]

Another finding in this trial is an increased local recurrence rate among patients in whom the bowel was perforated at surgery or in those patients in whom the margin of clearance was microscopically minimal. Similar results with an increased local recurrence rate after bowel perforation have been found in series of patients treated with surgery alone.[26,27] Whether a minimal margin of clearance is deleterious is more questionable. In a large series from St Mark's Hospital, no difference in the recurrence rate was noted comparing those with a microscopically minimal or unclear (less than 2 mm) margin of clearance to those with a larger margin.[28] In that trial, only the distal margin of clearance was taken into account. If, however, the specimen was carefully examined concerning the lateral spread, Quirke et al.[29] found that the local recurrence rate was increased if the lateral margin was not clear. In the present material, the doubtful microscopic clearance was either lateral or distal.

The radiation technique used in this trial differed from that used in most other trials. With three or four radiation portals, one can largely avoid irradiation of other parts of the pelvis and abdomen than the tumor-containing target volume. If the irradiation is given with two opposed anterior-posterior portals, as in most trials, the irradiated volume is considerably larger. This difference in the radiation technique could well explain the higher postoperative mortality rate noted in the Stockholm trial[8] and in the small trial from St. Mark's Hospital.[30] This was not observed in the present series. The increased postoperative mortality rate in the two mentioned series was restricted to patients older than 75 years and referred mainly to those with generalized disease at surgery. It is tempting to believe that a large irradiated volume may be deleterious in this age group. With the irradiation technique used in this trial, we have established that preoperative radio-

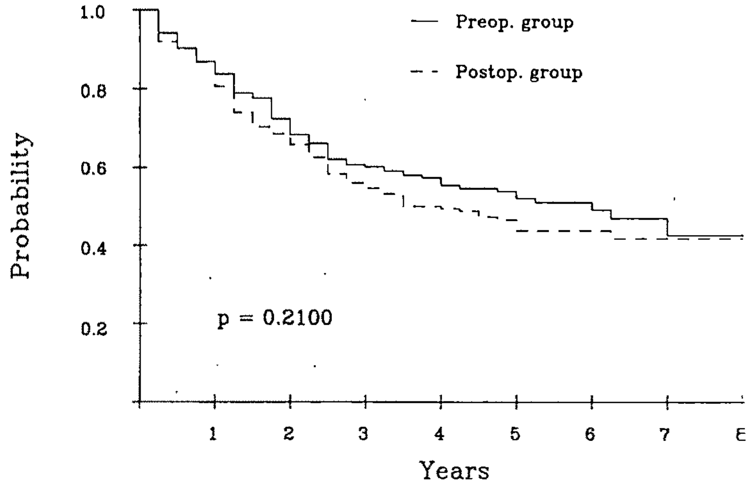

FIG. 6. Cancer-specific survival after curative surgery in the two treatment groups.

therapy to a high dosage level (CRE above 14.5) can be delivered without affecting the postoperative mortality rate. However, as in other trials[7,8] using preoperative radiotherapy, the postoperative morbidity was increased in one respect, *i.e.*, there was an increased frequency of infections in the perineal wounds after abdominoperineal resection. This increase in perineal wound sepsis prolonged the hospital stay. In the long term, however, this is no problem for the patient because the perineal wound healed within 3 months in virtually all patients.

Another question is whether additional therapy will cause a long-term increase in morbidity (intestinal obstruction, urinary or skin reactions). All patients with a minimum follow-up of 5 years in this trial were re-examined with respect to late adverse effects of radiation. After this follow-up evaluation, no differences were found between those who were given preoperative radiotherapy, postoperative radiotherapy, or surgery alone concerning bowel obstruction or other possible late adverse effects (manuscript in preparation).

The follow-up of this trial is still too short to estimate if there will be any survival benefits. Radiotherapy to the primary tumor area cannot affect occult metastases in the liver, for instance. On the other hand, if the local recurrence rate is decreased, and if such a recurrence is the only residual tumor, preoperative radiotherapy will, after a prolonged follow-up, have an impact on survival. In the Stockholm trial, when the survival curves were corrected for postoperative deaths, the survival was increased in the group of patients who received preoperative radiotherapy.[31] This difference is statistically significant. Similarly, in the EORTC trial, the survival curves are diverging with longer follow-up.[32] Taken together, however, the improvement of the local control by preoperative radiotherapy, even at higher dosage levels, does not translate into any substantially improved survival. This lack of any major survival benefit prompts the question of whether the radiotherapy should be postponed until a local recurrence has developed rather than be given to all patients before operation. The answer to this question is not known. However a local recurrence is usually a tragedy for the patient because of symptoms like pain, soiling, and/or fistulation. Local radiotherapy may give pain relief in most patients, whereas other symptoms respond less well. Also symptoms usually recur after a median time of 6 to 8 months. Radiotherapy, even if given at a very high dosage and combined with chemotherapy and/or surgery, is rarely curative; 5-year survival figures seldom excede 5%.[33-35] It is not known to what extent optimal treatment may keep a patient with a local recurrence locally symptom free for his or her remaining life span. The question whether preoperative radiotherapy for all patients is advantageous from a quality-of-life point of view, or if no additional radiotherapy at surgery but with an optimized treatment also including radiotherapy if a local recurrence develops is best, is addressed in an ongoing trial.

The data from this trial together with available data from the literature indicate that additional radiotherapy in patients with primarily resectable rectal carcinoma should be given before operation. This approach will be even more attractive if patients with a low risk of recurrence (such as Dukes' stage A cases) can be excluded before operation by transanal ultrasonography.[36,37]

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Ischemia Activates Neutrophils but Inhibits Their Local and Remote Diapedesis

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Hindlimb ischemia and reperfusion results in local limb and distant lung injury. This study tests whether the mechanism of injury is by ischemia mediated polymorphonuclear leukocyte (PMN) activation and diapedesis. Anesthetized rabbits were subjected to three hours of hindlimb ischemia ($n = 8$) or sham ischemia ($n = 4$). PMN derived solely from the reperfused ischemic limb and assayed flow cytometrically displayed an oxidative burst of 135 ± 8 fentamoles dichlorofluorescein (fmDCF)/cell compared to preischemic levels of 74 ± 14 fmDCF/cell ($p < 0.05$). Additional aliquots of isolated neutrophils were treated with phorbol myristate acetate (PMA) 10^{-7}M. In contrast to a 162% increase in oxidative burst before ischemia, neutrophils at ten minutes of reperfusion had an enhanced response to PMA of 336% ($p < 0.05$). Plasma collected from the ischemic hindlimb at ten minutes of reperfusion when introduced into an abraded skin chamber or intratracheally induced diapedesis in nonischemic animals. PMN accumulations in the skin chamber were 1636 ± 258 PMN/mm^3 after three hours ($n = 8$) compared to 63 ± 18 PMN/mm^3 induced by sham plasma ($n = 4$, $p < 0.05$). Introduction of ischemic plasma intratracheally into a lobar bronchus ($n = 4$) induced PMN accumulations after three hours, measured by bronchoalveolar lavage fluid of $19 \pm 2 \times 10^4$ PMN/mm^3 compared to $5 \pm 1 \times 10^4$ PMN/mm^3 with sham plasma ($n = 4$, $p < 0.05$). Diapedesis was completely prevented (0–3 PMN/mm^3, $p < 0.05$) by introducing ischemic plasma into skin chambers in animals whose hindlimbs had been made ischemic ($n = 6$) or into chambers located on skin regions that had been previously made ischemic ($n = 6$). Similarly after hindlimb ischemia, lavage of the lung with ischemic plasma yielded few PMN 0–3/mm^3 ($p < 0.05$). These data indicate that ischemia and reperfusion lead to generation of a circulating component in plasma that causes an oxidative burst in PMN and inhibits their diapedesis but promotes diapedesis when applied extravascularly to a naive animal.

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ISCHEMIA AND REPERFUSION induce polymorphonuclear leukocyte (PMN)-dependent tissue injury. Thus following lower torso ischemia, there is a prominent accumulation of leukocytes in, but not outside of, the pulmonary microvasculature.[1] Neutrophils are not seen in the lung interstitium and cannot be recovered by bronchoalveolar lavage (BAL). Furthermore neutrophils are not found with light microscopy in the tissue of the reperfused lower torso. Despite the physical absence of neutrophils in the interstitium it is believed that these cells mediate increased microvascular permeability.[2] We postulate that the reperfused tissue generates a factor(s) that enhances PMN activation, induces PMN adhesion in the microcirculation, but inhibits local and remote diapedesis.

To test this hypothesis, the PMN oxidative burst was assayed using flow cytometry after hindlimb ischemia. Furthermore plasma collected during reperfusion was introduced into abraded skin chambers or intratracheally into nonischemic animals to measure its effects on diapedesis. The same studies were conducted in ischemic animals to evaluate possible inhibition of PMN accumulations.

Materials and Methods

Animal Preparation

Forty-seven New Zealand white male rabbits weighing 3 to 6 kg were used. Initial anesthesia was achieved with intramuscular ketamine (35 mg/kg) and intravenous xy-

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lazine (5 mg/kg) and maintained with xylazine 2 mg/kg every 30 minutes. Saline, 0.3 mL/kg/hour was infused *via* a carotid arterial cannula placed aseptically *via* a small neck incision on the day of the experiment. All animals were placed on 37 C heating pads.

Hindlimb Ischemia

Anesthetized rabbits (n = 8) underwent three hours of bilateral hindlimb tourniquet ischemia. Cuffs were inflated to 160 mmHg. Before completion of the ischemic period, the vena cava was ligated just above the iliac confluence to ensure collection of blood derived solely from the ischemic region. Activated neutrophils are known to sequester in the lung microcirculation and if sampling were conducted from the systemic circulation might be unavailable for sampling. Moreover lung leukosequestration after reperfusion induces eicosanoid generation. This methodology excludes nonischemic tissue-derived metabolites. During the first ten minutes of reperfusion, the venous return of both hindlimbs was collected from the vena cava, distal to its point of ligation (approximately 0.5 mL/minute) and discarded. A similar volume of saline was simultaneously replaced *via* the carotid line. In previous studies by our laboratory, it was found that plasma thromboxane B_2 and leukotriene B_4 levels peaked ten minutes after reperfusion of the ischemic hindlimb, whereas immediate levels were not raised. Therefore after the ten-minute washout, 4 mL of hindlimb venous return was collected in cooled heparinized syringes containing 0.1 mL ethylene diamine tetracetic acid (0.07 mg/mL) and aspirin (0.05 mg/mL) and transferred on ice for flow cytometry. Thereafter another 10-mL sample of blood was collected in a similar manner and centrifuged at 1500 $\times g$ for 20 minutes. Aliquots of 0.5 mL plasma were frozen at −20 C and subsequently used in an *in vivo* chemotactic assay. Previous studies have shown that heparin, EDTA, or aspirin in doses used in plasma did not interfere with the chemotactic assay.

Sham Rabbits

Animals (n = 4) were prepared as above but were not subjected to ischemia.

Flow Cytometry

Intracellular generation of H_2O_2 by blood neutrophils was quantitated using flow cytometry and dichlorofluorescein-diacetate (DCFH). DCFH is a nonfluorescent compound that is oxidized to the highly fluorescent dichlorofluorescein (DCF) within neutrophils undergoing a respiratory burst. Leukocytes were isolated from blood using dextran sedimentation, 6% in 0.9% saline, (0.3 mL dextran solution per 3 mL blood) for 45 minutes at room temperature (Dextran T 500, Pharmacia, Piscataway NJ). In preliminary experiments, it was found that any centrifugation, vortexing, or even vigorous pipetting led to increases in baseline oxidation in neutrophils, so these procedures were eliminated in the final protocol. Aliquots of leukocyte-rich sediment (0.01 mL) were added to 1 mL of balanced salt solution (BSS). This solution contained NaCl (124 mM), KCl (5.8 mM), dextrose (10 mM), and hydroxyethylpiperazine ethanesulphonic acid (20 mM) and was titrated with NaOH to pH 7.4 before use. The BSS also contained DCFH (Molecular Probes, Eugene OR) and either buffer or phorbol myristate acetate (PMA) 10^{-7}M. The concentration of DCFH was 100μM, an amount that saturated leukocytes in samples from sham or experimental animals. After incubation for 20 minutes at 37 C the samples were placed on ice and analyzed with an Ortho Diagnostics System 2151 Cytofluorograf flow cytometer using the 488 ηm excitation line of an argon laser at 125 mw output. The PMN within each sample were identified by light scattering. After electronic gating, the green fluorescence of these cells in unstimulated and PMA-stimulated samples was quantitated (3000 to 5000 neutrophils per sample). In some experiments, the fluorescence values obtained by flow cytometry were calibrated with samples of pure rat neutrophils. These cells were obtained four hours after intraperitoneal glycogen. The cells were suspended in BSS, 10^6 cells/mL, and labeled with DCFH with or without PMA treatment. Measurements were conducted in a fluorometer (Perkin-Elmer, Norwalk, CT). Using a standard curve constructed with reagent grade DCF (Sigma Chemical, St. Louis, MO) the amount of DCFH oxidized to DCF by neutrophil H_2O_2 was quantitated, allowing conversion of the mean fluorescence channel number to fentamoles (fm) of DCF produced per cell, a value equivalent to fm of H_2O_2 produced per cell.

Skin Abrasion Blister Chambers

Chemotactic responses were measured by a modification of the technique of Otani.[3] After anesthesia, a 20 $\times$ 25 cm area of the back of the rabbits was clipped with electric shears (Wahl Clipper Co., Sterling, IL). These animals (n = 24) were only used to assay chemotaxis. The clipped region was coated with sodium thioglycolate (Lemon Scented Nair, Carter Products, New York, NY) for 15 minutes, washed with tap water, rinsed with 100 mL of 0.25% acetic acid, and then rerinsed with tap water. The animals were permitted to rest for 24 to 36 hours to allow any nonspecific inflammatory response to subside before chemotactic studies were performed. Animals exhibiting skin sensitivity were excluded from the study.

On the day of the experiment, the animal was reanesthetized and a circular area of hair-free skin was outlined with a template having a 9/32 inch diameter (Rapi-Design Template No. 40, Rapi-Design Products, Burbank, CA). This area was gently abraded with an electric ink eraser (Petty Electric Ink Eraser, Pierce Corp., River Falls, WI) until uniform glistening was produced. This normally took 15 to 20 seconds. The debris from the abraded area was removed by pressing adhesive tape (Blender M, 3M Surgical Products, St. Paul, MN) over the site. On rare occasions, when abrasion led to trace bleeding, the site was abandoned.

Plastic, unit-dose blister chambers (Rexhaus Corp., Westfield Industrial Park, Westfield, MA) with a volume capacity of 0.5 mL were placed over the abraded areas and secured with Steridrape (3M Surgical Products, St. Paul, MN). Usually 18 to 24 blister chambers could be affixed to each rabbit. Injections into the chambers were made with a 27-gauge needle. At the conclusion of the experiment, fluid was withdrawn from the chambers and neutrophils were counted with a hemocytometer. Animals were allowed to rest for 14 days before they were used again.

Plasma Aspiration

A tracheostomy was performed with a 7-mm tube. Through this tube a fine polyethylene cannula (internal diameter, 0.64 mm Delmed, Inc., Canton, MA) was introduced into the bronchus of the middle lobe of the right lung. Evans Blue dye 0.2 mg was added to the lavage solution for later confirmation of the location of the fine cannula. One milliliter of ischemic or normal plasma was introduced *via* the cannula into the bronchus of the middle lobe of the right lung and after five minutes the cannula was removed. Three hours later the animals were killed with an overdose of ketamine. A thoracotomy was performed and the left lung bronchus clamped. Bronchoalveolar lavage (BAL) was performed *via* the tracheostomy tube using three applications of 5 mL of saline. The BAL recovery of about 10 mL was centrifuged at 6000 rpm for five minutes (GCL-1 Centrifuge, Sorvall, Newton, CT). The pellet was suspended in 1 mL saline and PMN counted after Diff-Quik staining to identify macrophages (AHS del Caribe, Inc, Aguada, Puerto Rico).

Skin Capillary Blood Flow

This was measured using laser doppler (Laserflow Model BPM, No. 3, TSI, Inc., St. Paul, MN). The doppler signal produced an output proportional to blood flow, expressed in mL/100 g/minute.[4]

Experimental Protocol

Anesthetized rabbits were subjected to bilateral hindlimb ischemia ($n = 8$) or sham ischemia ($n = 4$) for three hours. After ten minutes of reperfusion the venous effluent was collected. PMN were separated and used for flow cytometry and the plasma used for blister and intratracheal treatments. The plasma was introduced into blisters on the animals whose hindlimbs had been made ischemic ($n = 9$), who had been subjected to sham ischemia ($n = 8$), or whose dorsal skin used for the blister preparation had been made ischemic with a Satinsky clamp ($n = 6$). Plasma collected from animals who had undergone sham ischemia was used as controls in all studies. Hindlimb or skin ischemia was for a period of three hours. Ten minutes of reperfusion was allowed before plasma was placed in the blister pack. In lung diapedesis studies, ischemic or sham plasma was introduced into the bronchus of the right middle lobe of animals subjected to three hours of hindlimb ischemia and ten minutes of reperfusion ($n = 8$) or sham ischemia ($n = 4$).

Data are expressed as mean ± SEM in text and figures. An analysis of variance, followed by a nonpaired Student's t test was used to determine significance between groups. Significance was accepted if p was less than 0.05.

Animals in this study were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and those prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (Department of Health, Education and Welfare, Publication No. 78-23 [National Institute of Health], revised, 1978).

Results

Neutrophils derived from the reperfused hindlimb displayed an oxidative burst of 135 ± 8 fmDCF/cell compared to preischemic levels of 74 ± 14 fmDCF/cell ($p < 0.05$). Additional aliquots of isolated neutrophils treated with PMA 10^{-7}M showed a 162% increase in H_2O_2 production before ischemia and an enhanced response of 336% after ischemia ($p < 0.05$, Fig. 1). Ischemic plasma, when introduced into abraded skin chambers or intratracheally, induced diapedesis in nonischemic animals. There were 1636 ± 258 PMN/mm^3 in the skin chambers after three hours compared to 63 ± 18 PMN/mm^3 induced by sham plasma ($p < 0.05$, Fig. 2). Introduction of ischemic plasma into the lung of nonischemic animals yielded, by BAL, accumulations of $19 \pm 2 \times 10^4$ PMN/mm^3 compared to $5 \pm 1 \times 10^4$ PMN/mm^3 induced by sham plasma ($p < 0.05$). In animals subjected to three hours of hindlimb ischemia and ten minutes of reperfusion, the ability of ischemic plasma to induce diapedesis in skin blisters or lungs was abolished. The recovery of PMN was 0–3/mm^3 in blister fluid and BAL ($p < 0.05$). Finally ischemic skin rendered prevented diapedesis induced by ischemic plasma introduced into blisters on the previously ischemic skin (0–3 PMN/mm^3, $p < 0.05$).

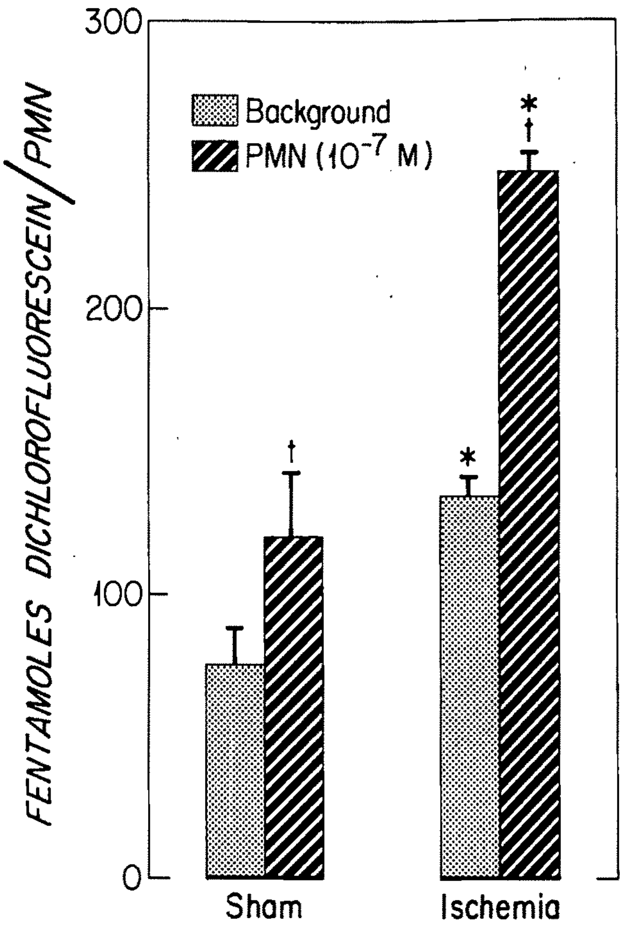

FIG. 1. Neutrophil H_2O_2 production measured flow cytometrically was enhanced following ischemia and by treatment with phorbol myristate acetate. Asterisks and daggers refer to significance ($p < 0.05$) between and within groups.

Skin Blood Flow

Baseline skin blood flow, measured with the laser doppler was 5.6 ± 0.18 mL/100g/minute. During hindlimb ischemia the dorsal abraded skin region showed increased blood flow of 6.8 ± 0.25, mL/100g/minute ($p < 0.05$). In one hour it had returned to baseline levels of 5.4 ± 0.14 mL/100 g/minute. During skin ischemia flow was reduced to 0.04 ± 0.01 mL/100 g/minute while after one hour of reperfusion flow increased to 6.4 ± 0.2 mL/100 g/minute ($p < 0.05$) and then returned to the preischemic levels of 5.7 ± 0.3 mL/100 g/minute.

Discussion

Ischemia and reperfusion lead to PMN-dependent injury. Recent studies have emphasized the role of PMN adhesion in modulating injury after reperfusion. Thus leukocyte-adherence receptor antibodies prevented adhesion and subsequent injury.[5,6] We postulate that ischemia leads to PMN activation, manifest by an oxidative burst and adherence receptor upregulation and that both phenomena mediate the reperfusion injury.

The first part of this study was designed to test the ability of reperfused tissue to increase PMN oxidative activity. Flow cytometry of PMN derived from the venous effluent of reperfused tissue demonstrated an increase in H_2O_2 production as well as an exaggerated response to a second stimulus, PMA. The mechanism of ischemia-induced PMN activation is unknown but may be *via* arachidonic acid derivatives. Thus leukotriene (LT) B_4 synthesized by reperfused tissue is a chemoactivator.[1] By stimulating a receptor site on the PMN surface, activation and an oxidative burst can ensue. In addition LTB_4 may stimulate leukocyte-adherence receptor expression.[7]

The second part of the study tested the ability of ischemic plasma to induce diapedesis. It was found that plasma derived from the ischemic hindlimb during reperfusion induced diapedesis in both abraded skin chambers as well as in the lungs of nonischemic animals. These data suggest that reperfused tissue generates a factor(s) that increases PMN-endothelial interaction. The ability of ischemic plasma to induce diapedesis when applied extravascularly may also be leukotriene dependent. Thus ischemic plasma contains increased levels of LTB_4, which is known to be both a powerful chemoactivator and chemoattractant.

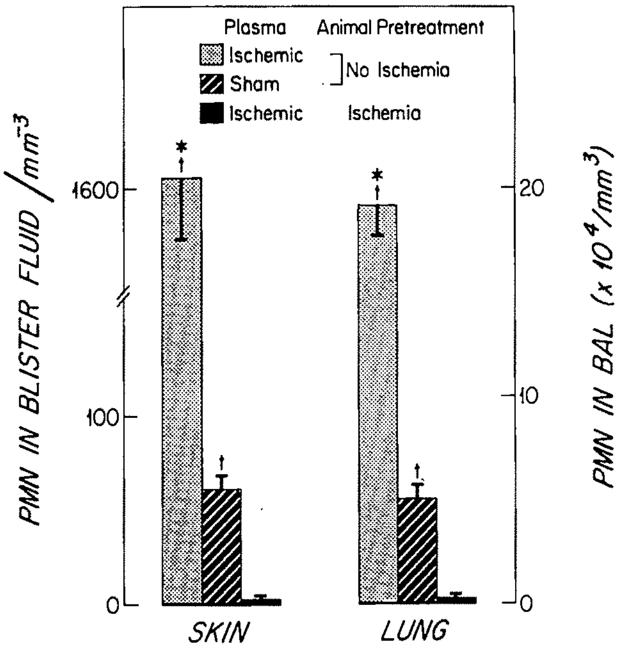

FIG. 2. PMN counts in skin blisters and bronchoalveolar lavage fluid were increased by ischemic plasma relative to sham plasma in animals that had not been made ischemic ($p < 0.05$) as indicated by asterisks. In contrast, when animals were subjected to hindlimb ischemia, diapedesis into skin blisters or lung was prevented even compared to sham plasma ($p < 0.05$) as indicated by daggers.

The third part of the study tested the effect of local and remote ischemia in moderating diapedesis. Surprisingly, after ischemia of skin, ischemic plasma with a known chemotactic ability could not induce diapedesis when instilled into blister chambers positioned on this previously ischemic skin region. Similarly, after hindlimb ischemia, ischemic plasma introduced by lavage into the lung or into the blister packs failed to induce diapedesis. It has been reported that mixing PMN with a chemoattractant will inhibit subsequent directed migration.[8] This is consistent with our observations that the intravascular administration of a chemoactivator induced by ischemia and reperfusion will inhibit a later chemotactic stimulus. These results suggest a desensitization of the neutrophil. Other interpretations are possible. Thus chemoactivators released intravenously may stimulate endothelium to synthesize prostaglandins that could serve as inhibitors of PMN adhesion and diapedesis. This is unlikely because neither indomethacin nor aspirin pretreatment of endothelial cells, to inhibit prostaglandin synthesis, prevented neutrophil adhesion.[9] Also, activated endothelial cells may generate a noncyclooxygenase-dependent leukocyte adhesion inhibitor.[10] Reports indicate that such an inhibitor acts directly on the leukocyte and is blocked by actinomycin D but not by indomethacin or aspirin. However it is unlikely that ischemic tissue synthesizes a leukocyte adhesion inhibitor because the time scale of synthesis of this stable protein is four hours.[10] In our study there was complete inhibition of diapedesis over the course of the first three hours after ischemia. Finally a low-flow phenomenon after hindlimb ischemia, induced by PMN plugging of the micro-circulation[11,12] of the skin or lung, is an unlikely cause of the inhibition of diapedesis. Histology of ischemic reperfused tissue (1) and skin blood flow measurements reported in this study and by others[13] discount this mechanism.

We speculate that the extravascular administration into lungs or blister packs of ischemic plasma will activate endothelium to synthesize intercellular adhesion molecules (ICAM) and/or endothelial leukocyte-adhesion molecules (ELAM). Thus *in vitro* or *in vivo* preincubation of endothelium with a chemoattractant increases PMN adhesion and diapedesis, events associated with ICAM or ELAM synthesis.[14–17] In contrast *in vitro* preincubation of PMN with leukotriene B_4, similar in effect to intravascular leukotriene B_4 administration or ischemia and reperfusion, will decrease PMN diapedesis through EC.[18] This desensitization suggests leukocyte adhesion receptor downregulation, or alternatively failure of induction of endothelial ICAM or ELAM. A recent study has described the sequence of neutrophil activation after hindlimb ischemia.[19] The oxidative burst and prominent additional response to PMA stimulation are noted after five minutes. At 30 minutes of reperfusion the neutrophils cannot be stimulated by PMA, whereas at 60 minutes the PMA effect has been restored to levels equal to those noted before ischemia. These results indicate that the timing of the second stimulus is important. It is possible that the chemotactic effect, blunted by hindlimb ischemia, would be restored after several hours. In a clinical setting, repeated episodes of ischemia may lead to long-term inhibition of chemotaxis and therefore vulnerability to sepsis. The observation of neutrophil migration into regions of myocardial or intestinal ischemia is not necessarily at variance with these considerations. It is likely that neutrophil desensitization is temporary[18] and with the continued presence of an extravascular chemoattractant, neutrophils will ultimately migrate.

Adhesion without diapedesis of activated neutrophils is sufficient to induce lung injury, documented by increased permeability. Studies in this laboratory have described the role of adhesion in mediating tissue injury after hindlimb ischemia. Eicosanoids, particularly leukotrienes and thromboxane A_2, as well as oxygen free radicals, appear to be important because their pharmacologic antagonists prevent lower-torso ischemia-induced lung leukosequestration and microvascular permeability increase.[20–24]

These data indicate that ischemia and reperfusion lead to the generation of a circulating agent in plasma that results in a PMN oxidative burst and inhibition of diapedesis. This is likely due to deactivation of the stimulated neutrophil because ischemic plasma, when applied extravascularly, enhances PMN migration.

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Immunologic Effects of Arginine Supplementation in Tumor-bearing and Non–tumor-bearing Hosts

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Supplemental dietary arginine has anti-tumor properties but the degree and mechanisms are unclear. In non–tumor-bearing CBA/J mice (n = 60), 1% arginine supplementation significantly enhanced thymic weight, spleen cell mitogenesis, and interferon-activated natural killer cell activity; no further enhancement was observed with 2% or 4% supplementation. Supplemental 1% arginine, when compared with 1.7% glycine, enhanced interferon-induced natural killer cell activity, lymphokine-activated killer cell generation, and macrophage cytotoxicity. In A/J mice (n = 420), bearing either a moderately immunogenic (C1300) or weakly immunogenic (TBJ) murine neuroblastoma, 1% arginine significantly ($p < 0.05$) retarded tumor growth and prolonged median survival time compared with glycine or no supplementation. Dietary arginine enhanced T-cell function and significantly increased responsiveness to autologous C1300 tumor in a mixed lymphocyte tumor cell culture (MLTC). The immunomodulatory effects of arginine provide nutritional and immunologic support of the tumor-bearing host and may be helpful when given concommitant with immunotherapy.

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ENTERAL AND PARENTERAL supplementation with the amino acid arginine has been demonstrated to have anti-tumor properties, both in chemically induced[1] and transplanted tumor models.[2] Underlying mechanisms have not been elucidated, although reduced tumor ornithine decarboxylase (ODC) activity[3] and elevated levels of tumor cyclic AMP[4] have been reported. It is not clear if these effects were directly mediated or occurred consequent to an altered immune response to the tumors. Recent evidence that supplemental arginine has immunostimulatory properties both in experimental animals[5] and in man,[6] suggested that observed anti-tumor effects may be mediated *via* a modulation of the host–tumor immune interaction.

The host–immune response to tumor is influenced by both natural cytotoxic mechanisms, in particular that mediated by natural killer cells[7] and macrophages,[8] and by antigen-specific immunity. The latter depends on the clonal expansion of cytotoxic T lymphocytes (T_{ctl})[9] in response to tumor-associated antigens (TAAs) recognized as foreign in association with self class II (Ia) antigens expressed on antigen-presenting cells such as macrophages or dendritic cells.[10] The expansion of specifically sensitized T_{ctl} is dependent on interleukin-2 production from activated T lymphocytes.[11]

The experimental objectives of these studies were threefold: first to determine the optimum immunostimulatory concentration of arginine; second to assess the anti-tumor effect of supplemental arginine and determine if this correlated with augmented concomitant immune responses; and third to determine if arginine supplementation influenced natural cytotoxic mechanisms and the potential for generation of lymphokine activated killer (LAK) cells.

Materials and Methods

Mice

Six-week-old male A/J [H-2^a], C57BL/6 [H-2^b], BALB/c (H-2^d), and DBA/2 (H-2^d) mice were obtained from the Jackson Laborotory (Bar Harbor, ME). Male Swiss Webster mice were purchased from Charles River Labs., Wilmington, MA.

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Diets

Diet in pellet form was obtained from Dyets (Bethlehem, PA). Purified pellet chow containing 24% casein protein (0.8% arginine) was used throughout these studies. Arginine and glycine were kindly provided by Sandoz Nutrition, Minneapolis, MN, and were prepared freshly each day at the indicated concentrations. The amino acid supplementation was administered *ad libitum* in the animals drinking fluid. Glycine 1.7% was used as the isonitrogenous control solution for 1% arginine.

Tumors

C1300 neuroblastoma (NB) arose from the spinal cord region of A strain mice in 1940 and it has since been maintained by serial *in vivo* and *in vitro* passage ever since. It is a weakly immunogenic tumor, as determined by excision–rechallenge experiments,[12] and is moderately sensitive to NK cell lysis *in vitro*. It expresses low but inducible amounts of MHC class I and class II antigens.[13] In contrast its clonal variant, TBJ-NRB, is poorly immunogenic as determined by these criteria and is not NK sensitive. P815, syngeneic to DBA/2, and YAC-1 lymphoma of A/Sn origin were maintained in continuous *in vitro* culture.

Medium

All assays, unless otherwise indicated, were performed in complete medium (CM), which consisted of RPMI 1640 (Gibco, Grand Island, NY) supplemented with 10% heat-inactivated fetal calf serum (FCS; Flow Laboratories Inc., Rockville, MD), antibiotics (penicillin 100 U/mL and 100 μg/mL streptomycin), 2mM L-glutamine and 5 $\times 10^{-5}$ 2-mercaptoethanol.

Reagents

Human recombinant interleukin-2 (rIL-2) was provided by Hoffman–La Roche (Nutley, NJ). Murine gamma interferon (rIFN -Γ) was provided by Genentech (South San Francisco, CA). Lipopolysaccharide (LPS; E.Coli K235) was obtained from List Biological Laboratories Inc., Campbell, CA.

Preparation of Single-Cell Suspensions

Single-cell suspensions of spleen and thymus were prepared by mechanical disruption followed by filtration through nylon mesh (Nytex: Tetko, Elmsford, NY). Cells were washed twice and resuspended in control medium.

Lymphocyte Proliferation Assays

Spleen (5×10^6/mL) or thymus (10×10^6/mL) cells suspended in 100 μL were added to 96-well, flat-bottomed microtitre plates: Conconavalin A (Con.A; Sigma Chemical Co., St. Louis, MO) was added to cultures at a final concentration of 5 μg/mL. For mixed lymphocyte cultures (MLR), allogeneic C57BL/6 spleen cells were irradiated (2000 Rads from a^{137} Cs source) and incubated with responder A/J spleen cells at a 1:1 stimulator:responder ratio in a total volume of 200 μL. In the mixed lymphocyte tumor cell culture (MLTC), autologous tumor cells were irradiated (5000 Rads) and added to responder spleen cells at a 1:10 stimulator:responder ratio. Cultures were incubated at 37 C in 5%CO_2 for 72 hours (Con.A) and 96 hours (MLR, MLTC). Eight hours before termination of the assay, wells were pulsed with 1.0 uCi of ^{3}H-thymidine (TdR; New England Nuclear; specific activity, 6.7 Ci/mL). Cells were harvested onto fiberglass filters (PHD: Cambridge, MA) and analyzed in a liquid scintillation counter. For mitogenic assays data is expressed as a stimulation index, a ratio of TdR incorporation into mitogen-stimulated and unstimulated wells. In the MLTC the stimulation index represents the ratio of TdR incorporation into wells containing autologous tumor as stimulator over wells that contain autologous spleen cells as stimulators. MLR data is expressed as the counts per minute of incorporated TdR.

Interleukin-2 Production

Measurement of IL-2 production 48 hours after stimulation with Con.A was performed as previously described.[5]

Generation of Lymphokine Activated Killer (LAK) Cells

LAK cells were prepared in 25 cm^3 tissue culture flasks by incubating erythrocyte-free spleen cells at a concentration of 5×10^6 cells/mL in 8 mL complete medium containing 200 μ/mL rIL-2 in 25cm^3. After three days of incubation at 37 C with 5%CO_2, cells were harvested and tested for lytic activity against YAC-1, C1300-NRB and P815 as described below.

Natural Killer Cell Assays

Fresh spleen cells were used to measure basal NK activity. For *in vitro* activation, spleen cells (5×10^6/mL) were incubated with gamma interferon (500 U/ml) in a total volume of 100 μL for 18 to 24 hours before the addition of ^{51}Cr-labeled YAC-1, and cytoxicity was measured in a 4-hour assay.

Cytotoxicity Assays

Labeling of targets for cytotoxicity assays was performed by incubation of 1×10^7 viable cells (YAC-1, C1300, P815) with 150 μL of Na^{51}CrO (2 mCi/ml; New England Nuclear, Boston, MA) for 90 minutes. The assay was performed in V-bottomed microwells by adding serial dilutions of effector cells to 1×10^4 ^{51}Cr-labeled target cells in a total volume of 200 μL CM. The plates were centrifuged (800 rpm × 5 minutes) at the beginning of the assay, incubated at 37 C in 5%CO_2 for 4 hours (NK, LAK) or 16 hours (macrophage), and centrifuged again (1200 rpm × 10 minutes). A volume of 100 μL was removed from each well for gamma counting. Percentage-specific lysis was computed according to the formula: (E-S) / (M-S) × 100, where E is the ^{51}Cr release in the presence of effector cells, S is the spontaneous ^{51}Cr release in the presence of medium, and M is the maximum release obtained by addition of the targets to an equal volume of 1% Triton X-100. The results are expressed as the mean percentage of lysis of triplicate experiments.

Macrophage Function

Measurement of Ia^k on peritoneal macrophages by indirect immunofluorescence was performed as previously described.[14] Determination of superoxide anion production from peptone-elicited PMA-stimulated peritoneal macrophages was measured as previously described.[5] Macrophage cytotoxicity was performed by a modification of the technique recently described.[15] Briefly, peritoneal cells from control mice or from mice pretreated four days previously with 1 mL of 10% proteose peptone were harvested in PBS and plated at different concentrations in 200 μL into 96-well tissue culture plates. After a four-hour adherence, nonadherent cells were removed and medium alone or medium containing 500 μ/mL of IFN and 1 μg/mL of LPS was added in a total volume of 200 μL. After incubating for 24 hours at 37 C and 5% CO_2, the medium was decanted and 200 μL of ^{51}Cr-labeled P815 tumor targets were added for an additional 16 hours of incubation. Cytotoxicity was measured by counting the ^{51}Cr-released in 100 μL aliquots. Data is expressed as percentage-specific tumor lysis as described above with the important exception that spontaneous release for the macrophage cytotoxicity assays is the amount of ^{51}Cr released by P815 cells on nonactivated macrophage monolayers. This we found to be considerably lower than spontaneous release from cultures without macrophages.

Amino Acid Analysis

Serum amino acids were measured by high-performance liquid chromatography.

Experimental Protocols

Experiment 1. Six-week-old CBA/J mice (n = 60) were fed ad libitum a 24% protein diet and were randomized to receive either 1%, 2%, or 4% arginine supplementation, or 1.7% glycine supplementation (isonitrogenous with 1% arginine) for a period of seven days.

Experiment 2. Six-week-old A/J mice (n = 480) were fed ad libitum a 24% protein diet for 1 week as shown in Figure 1. At this time (day 0), mice were innoculated subcutaneously in the right flank with 1×10^6 viable C1300-NRB or TBJ-NRB cells. They were immediately randomized to three equal groups receiving 1% arginine, 1.7% glycine, or no supplementation. Tumor volume [0.5 (length × width × height) was measured every three days until day 21 (TBJ-NRB) and day 24 (C1300-NRB), when tumor necrosis made evaluations unreliable. Duration of survival was recorded in 20 mice per group. Assays of immune function were performed in seven to ten mice per group at weekly intervals.

Experiment 3. Six-week-old CBA/J mice (n = 40) received a 24% protein diet for ten days and either 1% arginine or 1.7% glycine supplementation in their drinking fluid. At that time, mice were sacrificed for determination of NK cell function, LAK cell generation, and macrophage cytotoxicity.

Data Analysis

Statistical significance was computed using Student's t test for nonpaired data. Tumor growth curves were compared by analysis of variance (ANOVA). Data is expressed as mean ± standard deviation

Results

Experiment 1

Determination of the optimal concentration of supplemental arginine. The effects of arginine supplementation on thymic weight, spleen cell mitogenesis, natural killer cell activity, and macrophage function is shown in

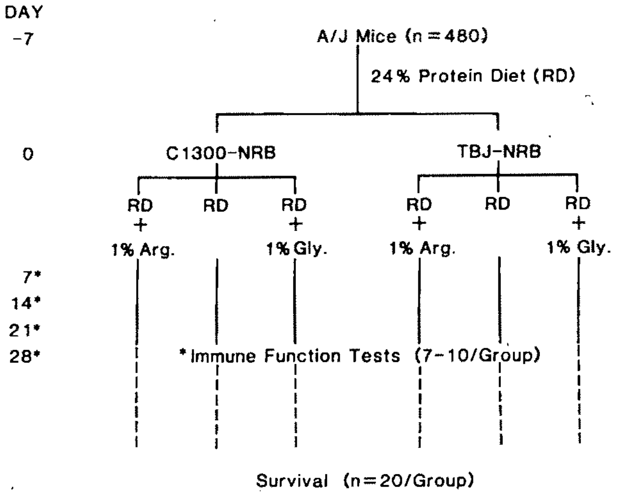

FIG. 1. Six-week-old A/J mice (n = 480) were fed a 24% protein diet (RD) for 7 days. Mice (n = 240) were innoculated with either C1300-NRB or TBJ-NRB on day 0 and were further randomized to continue on RD or to receive supplemental 1% arginine (Arg) or 1% glycine (Gly).

TABLE 1. *Dose-Response Effect of Arginine Supplementation on Immune Function**

Group	Thymic Wt. (mg)	Con A† (cpm × 10^{-3})	NK (basal) (% lysis)‡	NK (activated)§ (% lysis)‡	O_2-Production‖ (nmol/mg protein/90 minutes)
1.7% Glycine	42.3 ± 3	182.9 ± 13	13.7 ± 1	20.3 ± 4	185.3 ± 4
1% Arginine	53.4 ± 4	232.0 ± 10¶	13.6 ± 1	33.1 ± 15¶	208.6 ± 9
2% Arginine	49.6 ± 6	220.8 ± 15¶	14.6 ± 3	29.5 ± 9¶	237.0 ± 28
4% Arginine	44.1 ± 4	221.6 ± 11¶	13.2 ± 2	20.4 ± 1	187.6 ± 18

* CBA/J mice (n = 60) were fed a normal protein diet (24%) for seven days and received supplemental 1.7% glycine or arginine at 1%, 2% or 4% concentrations. Data represents mean ± SD.

† Spleen cells activated × 72 hours with con A.

§ Spleen cells activated *in vitro* with gamma interferon (500 u/mL).

‡ Percent cytotoxicity of YAC − 1 in a 4-hour ^{51}Cr-release assay at a 100:1 effector to target-cell ratio.

‖ Peptone-elicited peritoneal macrophages stimulated *in vitro* with PMA.

¶ $p < 0.05$ (Student's t test *vs.* 1.7% glycine).

Table 1. Both 1% and 2% arginine supplementation ($p < 0.05$) significantly augmented thymic weight, spleen cell mitogenesis, and inducible NK activity compared with both 1.7% glycine supplementation and the group receiving 4% arginine supplementation. No significant differences in basal NK activity or macrophage generation of superoxide anion were observed. In comparing plasma amino acid profiles from arginine-supplemented mice with results in control mice (Table 2), significant increases in arginine, ornithine, lysine, and proline levels were noted in all arginine-supplemented groups.

Experiment 2: Effect of 1% Arginine Supplementation on Tumor Growth and Anti-Tumor Immune Responses

A: C1300 NRB (immunogenic).

Effect of 1% Arginine supplementation on C1300 NRB growth and host survival.

Mice were injected on day 0 and received 1% arginine, 1.7% glycine supplementation, or no supplementation until death or sacrifice. The effect of arginine on tumor growth is shown in Figure 2. Arginine significantly ($p < 0.05$) reduced the mean tumor growth rate compared with both control groups. This reduction in tumor growth was associated with a prolongation of median survival from 45 days in both control groups to 58 days in arginine-supplemented mice ($p < 0.05$). Arginine did not significantly affect the tumor latency period (6 to 10 days) or tumor incidence (90%). No tumor regression was observed and all animals who developed tumor died of inanition secondary to local tumor burden without evidence of metastases. Mean carcass weight decreased with increasing tumor burden in all groups of animals. However no significant augmentation of mean carcass weight was observed in the arginine-supplemented group until the later stages of tumor growth as shown in Figure 3.

Effect of arginine on immune responses in mice bearing C1300-NRB.

The effects of 1% arginine supplementation in mice bearing C1300 NRB on thymic weight and immune function for more than 28 days is shown in Table 3: Compared with control groups, arginine-supplemented mice demonstrated significant ($p < 0.05$) enhancement of the mean thymic weight/carcass weight ratio at all time points. En-

TABLE 2. *Plasma Amino Acid Profiles* of the Dietary Group*

Conc. (μmol/L)	1.7% GLY	1% ARG	2% ARG	4% ARG
Glutamate	628 ± 11	628 ± 11	620 ± 5	526 ± 8
Proline	78 ± 4	132 ± 6†	195 ± 7†	110 ± 5†
Glycine	295 ± 5	159 ± 11†	157 ± 5†	132 ± 4†
Alanine	423 ± 5	522 ± 13	634 ± 11	415 ± 9
Valine	279 ± 5	361 ± 7	449 ± 6	365 ± 7
Leucine	220 ± 10	256 ± 5	275 ± 7	218 ± 7
Lysine	353 ± 15	492 ± 10†	632 ± 16†	365 ± 11
Isoleucine	131 ± 5	151 ± 4	153 ± 6	135 ± 8
Citrulline	52 ± 3	61 ± 3	66 ± 3	46 ± 3
Ornithine	61 ± 3	92 ± 5†	119 ± 5†	95 ± 3†
Arginine	108 ± 8	173 ± 8†	221 ± 5†	170 ± 10†

CBA/J mice were fed a 24% protein diet for 7 days and received 1.7% glycine supplementation or 1%, 2% or 4% arginine supplementation.

Values represent mean ± SD. of 3 values of pooled sera of mice (n = 5) in each group.

† $p < 0.05$ *versus* 1.7% glycine.

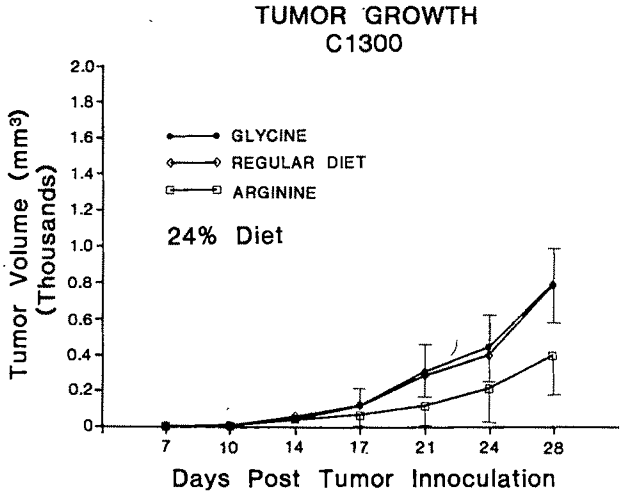

FIG. 2. Subcutaneous growth of C1300-NRB in A/J mice (n = 20/dietary group). $p < 0.05$ arginine *versus* glycine and regular diet groups, ANOVA.

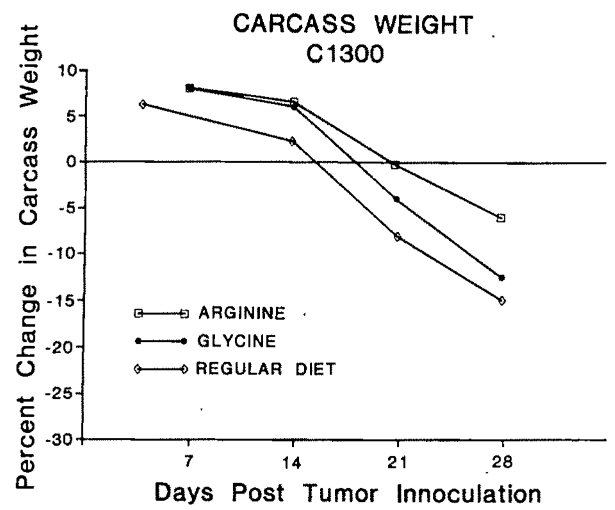

FIG. 3. Percentage change in carcass weight in mice (n = 40/dietary group) bearing C1300-NRB. $p < 0.05$ arginine *versus* glycine and regular diet groups, day 28 only.

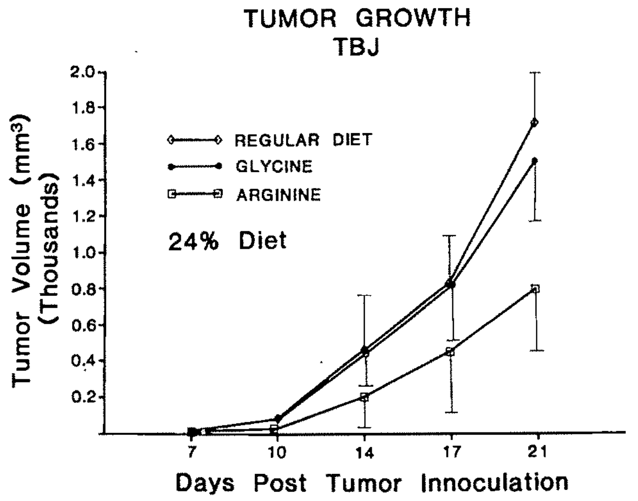

FIG. 4. Subcutaneous growth of TBJ-NRB in A/J mice (n = 20/dietary group). $p < 0.05$ arginine *versus* glycine and regular diet groups, ANOVA.

hanced nonspecific T-cell function was evident by an augmented mitogen-induced IL-2 production relative to control groups on day 7 after tumor inoculation ($p < 0.05$) The MLTC is a measure of tumor antigenicity and clonal proliferation of T lymphocytes in response to the antigen. Mice from arginine-supplemented subgroups consistently demonstrated significantly enhanced MLTC responses compared with control groups. This suggested that specific sensitization of T cells to tumor associated antigens may have occurred *in vivo.* We confirmed this by demonstrating antigen-specific cytotoxicity of C1300-NRB 14 days after tumor inoculation only in the arginine-supplemented group.

B: TBJ NRB (weakly immunogenic).

Effect of 1% arginine supplementation on TBJ-NRB growth and host survival.

In mice innoculated with the weakly immunogenic TBJ-NRB, there was a 100% incidence of tumors in all dietary groups with a mean latency period of 6 days. As

TABLE 3. *Effect of Arginine Supplementation on Immune Function in C1300-Bearing Mice**

Group	Day	Thymic Wt./Carcass Wt. (mg/gm)	MLR (cpm × 10^{-3})	MLTC† (S.I.)	Con A† (S.I.)	CTL‡ (% lysis)	IL-2§ (u/ml)	Ia‖ (%)
Arg	7	2.0 ± 0.2*	64 ± 10	5.9 ± 1.0*	123 ± 17*	ND	0.32 ± 0.12*	19 ± 2
Gly		1.4 ± 0.3	62 ± 12	3.6 ± 0.5	78 ± 22		0.17 ± 0.06	16 ± 3
RD		1.4 ± 0.2	62 ± 8	4.2 ± 1.0	77 ± 12		ND	ND
Arg	14	1.9 ± 0.3*	66 ± 8*	5.8 ± 0.8*	99 ± 10*	24 ± 2*	ND	ND
Gly		1.1 ± 0.2	53 ± 9	3.8 ± 0.5	75 ± 8	11 ± 2		
RD		1.1 ± 0.2	51 ± 8	3.8 ± 0.7	80 ± 8	11 ± 3		
Arg	21	1.7 ± 0.3*	56 ± 8	5.6 ± 1.0*	80 ± 7*	ND	ND	ND
Gly		1.1 ± 0.2	56 ± 10	3.6 ± 0.8	29 ± 4			
RD		0.9 ± 0.1	50 ± 7	3.5 ± 0.9	40 ± 3			
Arg	28	1.3 ± 0.2	53 ± 5*	5.7 ± 0.9*	21 ± 2*	ND	ND	ND
Gly		0.8 ± 0.1	47 ± 4	3.2 ± 0.4	10 ± 1			
RD		0.5 ± 0.1	41 ± 3	4.9 ± 1.1	9 ± 1			

ND, not determined.

* A/J mice (n = 240) were innoculated with tumor on day 0 and received 24% protein (RD) alone or with 1% arginine (Arg) or 1% glycine (Gly) supplementation; n = 7–12 mice/group/assay at each time point. Values denote mean ± SD.

† Lymphocyte proliferation to con A and mixed lymphocyte tumor cell cultures (MLTC) are expressed as stimulation indices (SI). Mixed lymphocyte reactions (MLR) are expressed as counts per minute (cpm) of ^{3}-H thymidine incorporation.

‡ CTL denotes cytotoxic T lymphocyte. CTL values represent cytotoxicity to C1300-NRB by spleen cells at a 100:1 effector to target-cell ratio in a 4-hour ^{51}Cr-release assay.

§ Values are units/ml of IL-2 production from con A-activated spleen cells.

‖ Percentage expression of Ia^k on peritoneal macrophages from C1300-bearing mice as determined by indirect immunofluorescence and FACS analysis.

$p < 0.05$ Arg *versus* Gly and RD.

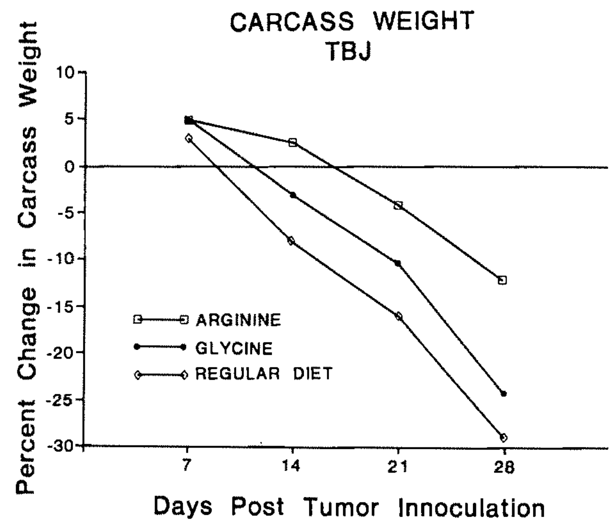

FIG. 5. Percent change in carcass weight in mice (n = 40/dietary group) bearing TBJ-NRB. $p < 0.05$ arginine *versus* glycine and regular diet groups, day 21 and day 28.

shown in Figure 4, tumor growth was significantly retarded by arginine supplementation compared with glycine supplementation and the regular-diet-alone group. This was associated with a prolongation of median survival from 25 days in control and glycine-supplemented groups to 36 days in arginine-supplemented mice ($p < 0.05$). As shown in Figure 5, mean carcass weight markedly decreased with increasing tumor burden, with arginine supplementation resulting in significant weight preservation at days 21 and 28 post-tumor inoculation when compared with both other groups.

Effect of arginine on immune responses in mice bearing TBJ-NRB.

Serial immune responses in mice bearing TBJ-NRB are shown in Table 4. Arginine-supplemented mice demonstrated significant preservation of mean thymic weight and IL-2 production relative to control mice. However unlike observations noted with C1300-NRB, no specific tumor sensitization could be demonstrated in MLTC and specific cytotoxicity responses.

Experiment 3: Effect of Arginine on NK Cell, LAK, and Macrophage Cytotoxicity.

The effect of arginine supplementation compared with isonitrogenous glycine in terms of cytotoxicity to C1300-NRB (which is moderately NK sensitive), YAC-1 (NK sensitive), and P815 (NK resistant) is shown in Table 5. Basal NK killing of targets was minimal and not significantly different between groups. *In vitro*-generated LAK cell responses and *in vitro*-activated NK killing of C1300-NRB was higher in arginine-supplemented mice compared with glycine controls (p = 0.05 and p = 0.09, respectively). Data is also shown indicating that activated macrophages from arginine-supplemented mice demonstrated greater lysis of P815 than glycine-supplemented mice. C1300-NRB was not a suitable target, however, for

TABLE 4. *Effect of Arginine Supplementation on Immune Function in TBJ-Bearing Mice**

Group	Day	Thymic Wt./Carcass Wt. (mg/g)	MLR (cpm × 10^{-3})	MLTC† (SI)	Con A† (SI)	CTL‡ (%)	IL-2§ (u/mL)	Ia‖ (%)
Arg	7	1.7 ± 0.3¶	71 ± 9	2.0 ± 0.2	103 ± 12¶	ND	0.8 ± 0.2¶	16 ± 1
Gly		1.4 ± 0.2	61 ± 6	1.4 ± 0.2	82 ± 14		0.4 ± 0.2	10 ± 2
RD		1.1 ± 0.2	64 ± 10	1.2 ± 0.1	80 ± 12		ND	ND
Arg	14	1.5 ± 0.3¶	73 ± 8*	2.5 ± 0.2	65 ± 9¶	0	ND	ND
Gly		1.0 ± 0.3	57 ± 5	1.6 ± 0.3	36 ± 3	0		
RD		1.0 ± 0.5	61 ± 9	2.2 ± 0.2	38 ± 4	0		
Arg	21	1.1 ± 0.2¶	51 ± 5	2.6 ± 0.2	65 ± 5¶	ND	ND	ND
Gly		0.7 ± 0.2	45 ± 4	1.9 ± 0.2	25 ± 3			
RD		0.7 ± 0.4	38 ± 3	2.1 ± 0.1	35 ± 4			
Arg	28	1.0 ± 0.3¶	54 ± 5	1.5 ± 0.2	10 ± 1¶	ND	ND	ND
Gly		0.5 ± 0.2	46 ± 8	1.5 ± 0.1	4 ± 1			
RD		0.4 ± 0.2	49 ± 9	1.4 ± 0.3	5 ± 1			

ND signifies not determined.

* A/J mice (n = 240) were innoculated with tumor on day 0 and received 24% protein diet (RD) alone or with 1% arginine (Arg) or 1% glycine (Gly) supplementation; n = 7–12 mice/group/assay at each time point. Values denote mean ± SD.

† Lymphocyte proliferation to con A and mixed lymphocyte tumor cell cultures (MLTC) are expressed as stimulation indices (SI). Mixed lymphocyte reactions (MLR) are expressed as counts per minute (cpm) of ^{3}H thymidine incorporation.

‡ CTL denotes cytotoxic T lymphocyte. CTL values represent cytotoxicity to TBJ-NRB by spleen cells at a 100:1 effector to target cell ratio in a four-hour ^{51}Cr-release assay.

§ Values are units/mL of IL-2 production from con A-activated spleen cells.

‖ Percentage expression of Ia^k on peritoneal macrophages from TBJ-bearing mice as determined by indirect immunofluorescence and FACS analysis.

¶ $p < 0.05$ Arg *versus* Gly and RD.

TABLE 5. *Effect of Arginine on NK Cell, LAK Cell, and Macrophage Cytotoxicity**

	Activated NK Cells†			LAK Cell Activity			Macrophages§
Group	YAC-1	C1300	P815	YAC-1	C1300	P815	P815
Arginine	33/9[‖]	24/5	0/0	64/56	60/38	54/26	55/ND
Glycine	20/4	17/4	0/0	59/55	52/28	46/19	37/ND
p	0.07	0.07	—		0.05	0.05	0.07

ND, not determined.

p value, Student's t test.

* CBA/J mice (n = 40) were fed a 24% protein diet for ten days with either 1% arginine or 1.7% glycine supplementation. Data is shown as mean percentage of cytotoxicity at a 100:1 and 25:1 (100/25) effector to target-cell ratio in 4-hour ^{51}Cr-release assays.

† Spleen cells were incubated with gamma interferon (500 μ/mL) for 18 hours.

‡ Spleen cells were stimulated with rIL-2 (200 μ/mL) for 72 hours.

§ Peritoneal adherent cells were stimulated with gamma-interferon (500 u/mL) and lipopolysaccharide (1 ug/mL) for 24 hours. Cytotoxicity of P815 was measured in a 16-hour ^{51}Cr-release assay.

‖ Values are Effector/Target.

macrophage cytoxicity experiments due to high spontaneous ^{51}Cr release.

Discussion

Individual amino acids are often described as essential on the basis of requirements for optimal growth and maintenance of positive nitrogen balance. Rose defined an amino acid as being essential when it cannot be synthesized from materials available to the cell at a rate commensurate with the needs for optimum growth of the species in question.[16] The amino acid arginine has traditionally been considered by these criteria to be a nonessential amino acid. Rose[17] determined, however, that in certain situations so-called nonessential amino acids were required in greater amounts and that the classification of arginine was a matter of definition. Recently Visek has suggested that nutrients such as arginine that are dispensable in normal animals may be classified as conditionally indispensable or essential when the physiologic state or metabolic impairment exceeds endogenous synthetic capacity.[18] In this respect, arginine has been demonstrated to be indispensable to the wounded or traumatized rat.[19]

Concomitant with this re-evaluation of the essentiality of individual amino acids for the entire organism, the concept of tissue-specific essentiality has arisen. Glutamine, for example, is a preferential fuel of the gastrointestinal mucosa[20] and the branched chain amino acids are avidly used by skeletal muscle.[21] Barbul[22,23] has reported on the thymotrophic effects of arginine, often most apparent in the stressed model, both after trauma or tumor bearing. Arginine *in vitro* is the only amino acid required for certain cytotoxic functions against tumor targets.[24] The possibility exists, therefore, that arginine may also have tissue-specific properties influencing components of the immune system. The experimental hypothesis underlying the studies reported here is that arginine supplementation can modulate components of the immune system both in an unperturbed host but more particularly in a situation in which the immune system is potentially compromised.

We initially demonstrated that 1% or 2% arginine supplementation significantly enhanced mitogenic responses and activated NK function compared with 1.7% glycine supplementation. No further enhancement was evident in the group supplemented with 4% arginine. The reason for this was not clear, but because plasma levels of arginine were not significantly increased in the 4% group, a reduced in-take probably accounted for the result.

Having established the relative efficacy of 1% arginine supplementation, we then addressed the hypothesis that arginine may mediate immunomodulatory activity in tumor-bearing animals, *i.e.*, it could influence tumor growth by modulating host–anti-tumor immune mechanisms. This approach is predicated on the presence of potentially immunogenic tumor-associated antigens against which the favorably modulated immune mechanisms may react. In mice bearing the moderately immunogenic tumor C1300-NRB, we observed that arginine supplementation retarded tumor growth and prolonged median survival. This was associated with significant preservation of thymic weight and augmentation of nonspecific immune function (IL-2 production). Furthermore antigen-specific MLTC responses and specific cytotoxicity were significantly increased by arginine compared with control groups. The underlying mechanisms behind these effects are unclear and they could relate to either enhanced tumor recognition through modulation of tumor or host class II MHC expression or through enhanced clonal proliferation of sensitized T lymphocytes. In *in vitro* studies using up to 1 mM arginine, we have not observed any modulation of MHC antigens on C1300 NRB or peritoneal macrophages In contrast we have recently reported an enhanced cytotoxic T-lymphocyte expansion, which suggests that the effects observed in this model were a consequence of modulation of host–responder lymphocytes.[5]

Arginine supplementation also produced anti-tumor effects in mice bearing the weakly immunogenic TBJ-NRB. The lack of immunogenicity of TBJ-NRB compared with C1300-NRB was evident by the lack of response in the MLTC. This low response may reflect the absence of a TAA-specific lymphocyte population, a requirement for growth factors (IL-2), or possibly the influence of suppressor mechanisms. Because nonspecific T-cell function, including IL-2 production, was enhanced in the arginine supplemented group, it is possible that IL-2-dependent anti-tumor immune mechanisms may have been influenced *in vivo* yet escaped detection by the *in vitro* assays we used. This explanation has not been proved at this time. It merits emphasizing, however, that a constant feature in arginine-supplemented mice in each tumor group was a relative preservation of immune function compared with control groups.

We next asked if arginine supplementation could modulate NK cell activity toward C1300 NRB or influence LAK cell generation and macrophage cytotoxicity, both of which require second signals, IL-2, and gamma interferon, respectively. We observed no direct enhancement of NK cell activity to YAC-1 or C1300-NRB. However, interferon-activated NK activity was considerably enhanced in arginine-supplemented mice when compared with glycine-supplemented mice. LAK cell generation, which is now considered by most authorities to represent expansion of cells with the NK phenotype in response to IL-2,[25] was consistently increased in the arginine-supplemented animals. This is consistent with our previous observations that the effect of arginine on cellular components of the immune system *in vivo* and *in vitro* appears to permit an enhanced responsiveness of the cells to lymphokines.[5] The lack of specificity or arginine when compared with glycine control groups was evident because macrophage cytotoxicity was also enhanced. Interestingly Hibbs et al.[26] recently reported that L-arginine is essential for macrophages to demonstrate a cytotoxic effector activity mechanism being linked to the conversion within macrophages of arginine to citrulline and nitrite by the enzyme arginine deiminase

The mechanism of action of arginine is unknown. Arginine is a secretagogue of growth hormone,[27] insulin,[28] and prolactin,[29] all of which may positively influence immune responses.[30,31] Arginine exerts a number of functions at the cellular level: all tissues use arginine for cytoplasmic and nuclear protein synthesis; arginine is involved by its guanidino group in NAD-dependent ribosylation reactions, *e.g.*, the activation of adenylate cyclase, thus potentially altering the cellular content of cyclic nucleotides;[32] arginine may be converted to citrulline and nitrates;[33] arginine is converted by the enzyme arginase (high activity in activated macrophages) to ornithine, and ornithine itself has been demonstrated to have potent effects on the immune system.[34] Arginine (and ornithine) are precursors of the polyamines putrescine, spermine and spermidine, which are low–molecular-weight compounds required for optimum cell growth and differentiation.[35]

These studies demonstrate that arginine has the properties of a nonspecific immunomodulator and has immunopreserving capacity. These properties, which appear separate from nutritional effects, have potential clinical applicability in the cancer patient as an adjunct in immunotherapy; as an adjunct to patients who are malnourished requiring nutritional support during radiotherapy or chemotherapy; and as an adjunct in patients with impaired immune reactivity, which often occurs in head and neck cancer patients.

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HIV-1–Associated Thrombocytopenia

The Role of Splenectomy

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Thrombocytopenic purpura is a common hematologic abnormality occurring in individuals infected with the human immunodeficiency virus, HIV-1. Of the nearly two million people infected with HIV-1, approximately 11% have platelet counts of less than 100,000/mm^3. If no etiology other than HIV-1 infection can be found for the thrombocytopenia, the syndrome is referred to as HIV-1–associated thrombocytopenia (HAT). Steroids lead to an improvement in the platelet count in 60% to 80% of effected individuals, but the majority of those who respond cannot maintain a normal platelet count when steroids are withdrawn. Furthermore concern over chronic steroid therapy in HIV-1–infected individuals has led to the investigation of other forms of treatment for this syndrome. This report describes the experience at Duke University Medical Center with eight patients who developed HAT and subsequently underwent splenectomy. In this group there was 1 complete response, 5 partial responses, and 2 patients who did not respond. There were no perioperative deaths and minimal perioperative morbidity. No evidence for the progression of HIV-1 infection in asymptomatic patients after splenectomy to AIDS related complex (ARC) or to the acquired immune deficiency syndrome (AIDS) was seen. In addition no increase in the susceptibility to infections by encapsulated organisms as a result of splenectomy was observed after a mean follow-up of 13.25 months. A review of 79 other cases reported in the literature suggests a higher response rate than that observed in our patients. Reasons for this discrepancy are discussed and an algorithm defining the role of splenectomy in the management of HAT is presented.

THROMBOCYTOPENIA IS A COMMON hematologic abnormality that occurs in individuals infected with the human immunodeficiency virus, HIV-1. Of the nearly two million people in the United States with HIV-1 infection,[1] approximately 11% have platelet counts of less than 100,000/mm^3.[2] Within this group, approximately 10% of healthy HIV-1 seropositive patients (Walter Reed stages 1 and 2) and 30% of those with the acquired immunodeficiency syndrome (AIDS) or AIDS related complex (ARC) may have clinically significant symptoms from their thrombocytopenia.[3] However life-threatening bleeding episodes are rare. Interestingly 18% to 32% of patients with platelet counts greater than 30,000/mm^3 and 6% to 8% of those with platelet counts less than 30,000/mm^3 experience a spontaneous remission of their thrombocytopenia.[4,5] In addition to its relatively benign clinical course, HIV-1–associated thrombocytopenia (HAT) does not indicate progression of the immune deficiency.[6,7]

Despite the clear association between HIV-1 infection and thrombocytopenia seen in many studies of intravenous drug addicts,[8] hemophiliacs,[9] and homosexuals,[10] the etiology of HAT remains unclear. Several researchers have suggested that high levels of platelet-bound IgG and circulating immune complexes may be the cause of the thrombocytopenia.[10-12] Other investigators have found high titers of antibodies that bind a 25,000 D antigen in the platelet membrane of some individuals with HAT.[13] This platelet membrane antigen was not detected on other hematopoietic cells and was distinct from the core proteins of HIV-1. The inability to find this platelet membrane antigen in all HIV-1–infected individuals with HAT suggests that multiple mechanisms may be involved in the underlying pathophysiology of the syndrome.

The frequency of spontaneous remissions and the undefined mechanisms of HAT have made development of

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a uniform treatment plan difficult. Therapeutic options have included steroids, intravenous immunoglobulin (IVIG), danazol, vincristine, and splenectomy.[4,5,14–19] Unfortunately none of these treatments have been consistently successful and many may increase the degree of immunosuppression in patients whose underlying pathology is an acquired immunodeficiency. Steroids initially seemed to be the most promising because they led to a rise in the platelet count in 60% to 90% of patients in whom they were tried.[4,14] Increases in patient platelet counts, however, were rarely maintained when steroids were withdrawn. More recently splenectomy has been recommended by some as the treatment of choice[18] as a result of encouraging short-term results. However review of the experience at Duke with splenectomy for HAT suggests that the effectiveness of this procedure is unpredictable. Based on this series and a review of the literature, the following report attempts to establish the safety of splenectomy in HIV-1–infected individuals and to define its role in those seropositive patients who become thrombocytopenic.

Materials and Methods

Eight patients who were HIV-1 seropositive and who underwent splenectomy at Duke University Medical Center were reviewed. All patients had thrombocytopenic purpura and were managed by a multidisciplinary team with regular follow-up examinations. Seven of the eight patients had an elevated antiplatelet antibody titer, a normal or increased number of megakaryocytes in their bone marrow, and no other identifiable cause for their thrombocytopenia except for HIV-1 infection. The eighth patient, although thrombocytopenic, also had a Coomb's positive hemolytic anemia for which he underwent splenectomy. The splenectomies in this study were performed between 1986 and 1988.

The effect of splenectomy on the patient's platelet count was categorized as complete, partial, or no response. A complete response was defined as a sustained increase in the platelet count to more than 150,000/mm^3 during the entire follow-up period. A partial response was defined as an increase in the platelet count by more than 50,000/mm^3 from preoperative values, but to a peak value of less than 150,000/mm^3, or a platelet count that fell at any time during follow-up to between 50,000/mm^3 and 150,000/mm^3. No response was defined as a platelet count that failed to rise by more than 50,000/mm^3 after operation or one that fell during the follow-up period to less than 50,000/mm^3. Standard deviations for platelet counts and other descriptive data are recorded in parentheses throughout the text.

Results

Between 1986 and 1988, seven men and one woman who were seropositive for HIV-1 underwent splenectomy at Duke University Medical Center. The average age of this group of patients was 40.6 years (range, 30 to 79 years). Six of the seven men were homosexuals. The seventh acquired his HIV-1 infection through a blood transfusion. The single female patient had a frequent sexual partner who was an intravenous drug abuser.

At the time of presentation five patients had asymptomatic HIV-1 infection, one patient had ARC, and two patients had AIDS. Presenting symptoms relating to the thrombocytopenia are shown in Table 1. Bruising, purpura, and/or petechiae were the most common findings. Two patients had evidence of mild lower gastrointestinal bleeding with hemoccult-positive stools. However both of these patients had a normal hemoglobin and hematocrit. Three patients were anemic at the time of presentation. Two had evidence of hemolytic anemia and the third had an anemia of chronic disease. The most serious bleeding manifestation of the thrombocytopenia was a hemarthrosis that occurred in one individual. None of the patients had a history of a major bleeding episode severe enough to cause hemodynamic instability. Nonhematologic signs or symptoms included recent fevers reported by four patients and splenomegaly found in two patients

TABLE 1. *Presenting Characteristics of Patients with HIV-1-Associated Thrombocytopenia*

Patient	Age	Sex	Stage	Presenting Signs and Symptoms	Hb/Hct	Platelet Count/mm^3
1	40	M	Asymptomatic	Guaiac positive stools, epistaxis, fevers	13.2/42	17,000
2	79	M	AIDS	Bruising, guaiac positive stools	13.9/43	13,000
3	32	M	Asymptomatic	Bruising	15.6/45	9000
4	41	M	ARC	Fevers, splenomegaly	8.4/25	90,000
5	31	M	AIDS	Petechiae, purpura, gingival hemorrhage, splenomegaly, hemarthrosis, fevers	8.4/26	13,000
6	34	M	Asymptomatic	Bruising, petechiae, purpura	16.4/48	14,000
7	38	M	Asymptomatic	Bruising, petechiae	15.1/44	3000
8	30	F	Asymptomatic	Petechiae, hematuria, gingival hemorrhage, fevers	6.8/22	8000

TABLE 2. *Effect of Treatment on Platelet Count*

		Platelet Counts*					
Patient	Preoperative Treatment	Lowest Preop.	Immediate Preop.	At Discharge	Follow-up (Range)	Current (Response)†	Months of Follow-up
1	Steroids, platelets	17,000	20,000	44,000	24,000–47,000	24,000 (NR)	18
2	Steroids	13,000	37,000	358,000	124,000–239,000	239,000 (PR)	18
3	Platelets	9000	9000	669,000	78,000–669,000	91,000 (PR)	11
4	ZDV	90,000	90,000	105,000	103,000–532,000	456,000 (PR)	14
5	Platelets	13,000	110,000	45,000	10,000–174,000	20,000 (NR)	12 (dead)
6	Steroids	14,000	183,000	344,000	143,000–322,000	144,000 (PR)	25
7	IVIG	3000	97,000	689,000	78,000–1,172,000	111,000 (PR)	6
8	Steroids, platelets, IVIG	8000	371,000	676,000	—	347,000 (CR)	2

* Units are platelets/mm^3.

† Response recorded as CR (complete response), PR (partial response), and NR (no response).

All eight patients received some form of treatment before surgery in an attempt to increase their platelet counts. These medical interventions shown in Table 2 included steroids, 3′-azido-2′, 3′-dideoxythymidine (formerly abbreviated AZT, now referred to as zidovudine or ZDV), intravenous gamma globulin (IVIG), and platelet transfusions. Steroids, used in four patients, increased the preoperative platelet count sufficiently to obviate the need for perioperative blood product transfusion in two individuals. The remaining two patients who received steroids, however, still required platelet transfusions during surgery. Two additional patients received perioperative platelet transfusions as their sole form of treatment. IVIG led to a marked elevation in the platelet count of both individuals in whom it was tried; by itself in one, and in conjunction with steroids and platelets in the other. ZDV helped stabilize the platelet count in one patient. These preoperative treatments, as a group, were successful in raising platelet counts from an average of 20,875/mm^3 (± 28,261) to 114,625/mm^3 (± 118,006) immediately before splenectomy.

All eight patients underwent splenectomy *via* a left subcostal incision. The operative findings are summarized in Table 3. An accessory spleen was found in one patient. There were no intraoperative complications. Average blood loss for the eight cases was 351 cc (± 336 cc). Average spleen size was 381 g (± 263 g). Splenic pathology was normal in three cases and revealed slight congestion with focal reactive hyperplasia in the remaining five cases.

All eight HIV-1—seropositive patients who underwent splenectomy tolerated the procedure well. The postoperative complications and length of hospital stay are listed in Table 3. There were no perioperative deaths and the only major complication was a pancreatic tail injury in a patient who had cirrhosis of the liver. This complication led to the development of a retroperitoneal fluid collection, with subsequent pancreatitis, pancreatic fistula, and ascites. However this patient was discharged on the eighth postoperative day and successfully treated with conservative management as an outpatient. There were several minor postoperative complications. Three patients developed postoperative fevers secondary to atelectasis. An additional patient developed a fever in conjunction with a pelvic vein thrombosis secondary to pelvic inflammatory disease. One patient became disoriented on the night after surgery presumably secondary to his pain medication, and

TABLE 3. *Operative Findings, Complications and Hospital Course*

Patient	Spleen Weight (g)	Accessory Spleen	Estimated Blood Loss (cc)	Complications	Hospital Stay (Days) PostOp.
1	200	No	1,000	Retroperitoneal fluid collection, Pancreatitis, Pancreatic Fistula, Ascites, Fever, Atelectasis	8
2	200	No	660	None	9
3	400	No	200	Stitch Abscess 21 days (*Staphylococcus Epidermis*) postoperatively	5
4	1,000	No	100	Disorientation, Fever	5
5	370	No	500	Fever	8
6	250	No	150	None	6
7	380	Yes	100	None	5
8	250	No	100	Fever	9

another patient developed a stitch abscess after discharge from the hospital (21 days after operation) from which *Staphylococcus epidermidis* was isolated. The average postoperative hospital stay was 7.6 (± 3.4) days.

The postsplenectomy platelet counts are shown in Table 2. The initial response to splenectomy was rapid. Six of the eight patients had platelet counts greater than 100,000/mm^3 at the time of discharge. During follow-up platelet counts fluctuated considerably. After a mean follow-up of 13.25 months, however, only one patient can be categorized as having had a complete response to splenectomy alone. Five patients have had a partial response to splenectomy and two have shown no response. In this group of patients there was no correlation between either preoperative clinical status or preoperative platelet count and the eventual response to splenectomy.

After operation seven of the eight patients required further medical treatment. Three patients were started on ZDV. Two of these patients (one with ARC and one with AIDS) received ZDV for symptomatic HIV-1 infection with low absolute CD4 counts when their platelet counts had decreased to less than 150,000/mm^3. Once they started taking ZDV, their platelet counts rose to more than 150,000/mm^3. These two patients, because they are still on ZDV, are listed in Table 2 as partial responders to splenectomy, even though their current platelet counts are more than 200,000/mm^3. The third patient with asymptomatic HIV-1 infection was started on ZDV because his platelet count decreased to less than 100,000/mm^3 after splenectomy. Even on ZDV this patient's platelet count remains less than 100,000/mm^3. Of the five patients who received steroids, two were receiving perioperative coverage and their steroids could be tapered rapidly. The three other patients (two nonresponders and one partial responder) are still on steroids in an attempt to maintain their platelet counts. Despite therapy, none of these three patients' platelet counts have returned to normal.

Progression of HIV-1 disease has occurred in two of the eight patients to date. One patient progressed from ARC at the time of surgery to AIDS approximately 4 months after surgery. The other patient who had AIDS at the time of splenectomy died 12 months later of disseminated *Mycobacterium avium-intracellulare* infection. The five asymptomatic patients have had stable absolute CD4 cell counts and CD4/CD8 lymphocyte ratios throughout the follow-up period.

Discussion

Thrombocytopenic purpura is common in HIV-1–infected individuals and occurs at all stages of disease. Unlike idiopathic immune thrombocytopenic purpura (ITP) in which abnormal bleeding is the most common presentation,[20,21] HAT is usually well tolerated despite very low platelet counts.[18] Because the natural history and underlying pathophysiology are poorly understood, no uniform consensus has emerged on how to best manage HAT. Some physicians have elected to adopt a course of observation without medical treatment, while others have attempted a variety of treatments including steroids, IVIG, danazol, vincristine, ZDV, and/or splenectomy. Although many of these treatments work well in idiopathic ITP, their effectiveness in HAT may be undermined by their potentially deleterious effects in an immunocompromised host.

Of the treatments listed above, steroids have been used most frequently in HAT. Several studies have shown them to be effective in raising platelet counts in 60% to 90%[4,14] of HIV-1–infected individuals with thrombocytopenia. Unfortunately most of these patients cannot maintain an adequate platelet count when steroids are withdrawn. In addition long-term steroid therapy may have several potentially deleterious effects in HIV-1–infected individuals. First because of their documented effects on T-cell function, steroids may further suppress immunologic integrity, leading to an increase in opportunistic infections.[22] Second steroids may accelerate the progression of HIV-1 disease to AIDS by suppressing the body's protective immune response against the virus. Finally steroids can be harmful to individuals with chronic active HBsAg-positive liver disease.[23,24] Because 20% to 30% of HIV-1–infected individuals are HBsAg positive,[25,26] steroids as a first line treatment for these individuals would be contraindicated. These concerns have increased the interest in splenectomy as a treatment for HAT.

Eight HIV-1–infected patients have undergone splenectomy at Duke University Medical Center with no perioperative deaths or major infectious complications. This experience documents the safety of splenectomy in HIV-1–seropositive individuals. The most serious noninfectious complication in this series was related to an unrecognized pancreatic tail injury at the time of surgery in a patient with underlying liver disease. The average hospital stay was short and all patients returned to their preoperative functional levels. Although the initial response to splenectomy was rapid with six of eight patients having platelet counts of more than 100,000/mm^3 at the time of discharge, marked fluctuation in patient platelet counts occurred during follow-up. In addition the prolonged maintenance of platelet counts greater than 150,000/mm^3 was uncommon. Overall, of the six responders in this series, one had a complete response and the remaining five had partial responses.

Several reports have suggested that splenectomy is a safe, effective procedure in HIV-1–infected individuals with thrombocytopenia.[4,5,14–19] These reports, summarized in Table 4, show that in the 79 reported cases of

TABLE 4. *Summary of Reported Cases*

Series	Number of Patients	Average Age	Mean Preop. Platelets*	Complications	Response‡			Follow-up (Months)
					(CR)	(PR)	(NR)	
Schneider[17]	15	33.3	15,933	1 Pan-cut fistula, 1 pneumococcal pneumonia, 1 wound infection	9	6	0	12.4
Oskenhendler[15]	14	28.7	8643	1 Pneumonia and meningitis	6	4	4	10
Ferguson[18]	11	32.6	19,700	2 wound seromas	11†		0	12.4
Walsh[4]	10		16,000	None reported	10	0	0	10
Goldsweig[5]	7	34.9	11,714	None reported	6	1	0	14
Abrams[14]	15			None reported	10	0	5	—
Costello[16]	3	37	7333	None reported	1	1	1	20.6
Rosenfelt[19]	4		30,000	None reported	2	1	1	—
Present Series	8	40.6	20,875	See Table 3	1	5	2	13.25
Total	87				74 (85.1%)		31 (14.9%)	

* Units are platelets/mm^3.

† Differentiation between complete and partial response not made.

‡ Response reported as CR (complete response), PR (partial response), and NR (no response).

HAT for which splenectomy was performed (excluding the Duke series), there were no deaths and only five significant postoperative complications. The overall complete and partial response rate was 86.1% (68 of 79 patients). In the Duke series, there was a 75% (6 of 8 patients) overall complete or partial response rate. Interestingly the Duke series was the only one in which the number of patients with a partial response outnumbered those with a complete response. Several factors may influence the response to splenectomy in HIV-1–infected individuals and account for the differences between reported series. These factors include the duration of thrombocytopenia before splenectomy, the platelet response to steroids, the patient's stage of HIV-1 infection, and/or the titer of antiplatelet antibodies. In addition not only did definitions for platelet responses to splenectomy vary among studies but frequently too little information was given in these reports to allow a meaningful assessment of the relative importance of the various individual factors.

One report suggested that the platelet response to preoperative steroids is predictive of the response to splenectomy.[16] Although there were not enough patients in that series to determine statistical significance, our results in four patients who were treated before operation with steroids appear to support this contention. Two patients achieved a complete response with steroids before surgery. After splenectomy one maintained a complete response and the other achieved a partial response. Two other patients did not respond to steroids before surgery. After splenectomy one had a partial response and the other had no response.

It is interesting that there has been only one report of an accessory spleen (the one in this series) in patients with HAT. The role of accessory spleens in patients who respond poorly to splenectomy remains to be determined. However none of the patients in this series have had an accessory spleen documented by radionucleotide scan after operation.

The overall complication rate for splenectomy in patients with HAT is very low (6%) and there have been no reported perioperative deaths. Interestingly, although the operative mortality and morbidity rates for splenectomy in patients with idiopathic ITP are higher,[27–30] the overall reported response rates of thrombocytopenic patients with and without HIV-1 infection to splenectomy are comparable.[28] However, as exemplified in the current series, the degree of platelet-count fluctuation in HIV-1–infected individuals after splenectomy is greater, leaving a higher percentage of these patients with only a partial response. Therefore, while well tolerated by HIV-1–seropositive individuals, the use of splenectomy for HAT must be determined on a case-by-case basis because of its unpredictable outcome and still-undefined long-term consequences.

In view of our results with splenectomy in HIV-1–infected patients and our experience in treating this problem medically, we have developed the following algorithm for managing HAT (Fig. 1). Patients presenting with refractory thrombocytopenia are evaluated with antiplatelet antibodies and have a bone marrow examination. If no clear etiology can be found for the thrombocytopenia, the presence of elevated anti-platelet titers and normal or increased numbers of megakaryocytes in the bone marrow usually suggests the diagnosis of ITP. However if the patient is seropositive for HIV-1 infection, the diagnosis of HAT is made.

Underlying our approach to individuals with HAT is an attempt to be as conservative as possible. Patients with no signs or symptoms of bleeding are considered to be asymptomatic. Because HAT is well tolerated, we rec-

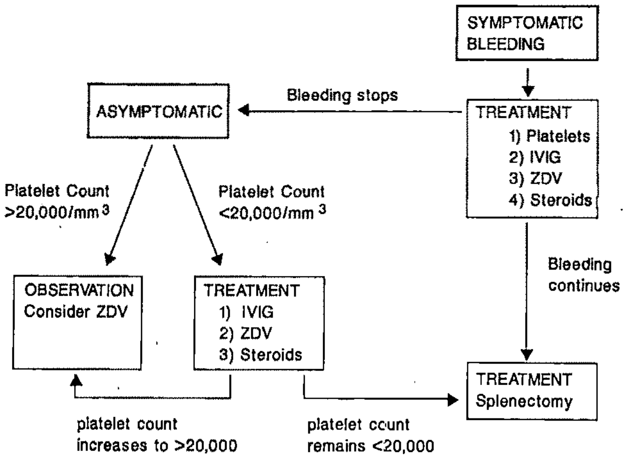
SYMPTOMATIC BLEEDING
ASYMPTOMATIC
Bleeding stops
TREATMENT 1) Platelets 2) IVIG 3) ZDV 4) Steroids
Platelet Count >20,000/mm3
Platelet Count <20,000/mm 3
Bleeding continues
OBSERVATION Consider ZDV
TREATMENT 1) IVIG 2) ZDV 3) Steroids
TREATMENT Splenectomy
platelet count increases to >20,000
platelet count remains <20,000

FIG. 1. Algorithm for the treatment of patients with HIV-1-associated thrombocytopenia.

ommend close observation with no medical therapy if the platelet count is greater than 20,000/mm^3. Such an approach allows spontaneous remissions[4,5] and avoids the potential risks of treatment with ZDV and/or steroids. For those patients with no signs or symptoms of bleeding and platelet counts of less than 20,000/mm^3, a more aggressive medical regimen is followed. We start either ZDV (200 mg every four hours), steroids (1 mg/kg/d), or both, reserving IVIG (.4-2 g/kg/d) for patients with platelet counts of less than 10,000/mm^3.

There are several reports of increases in circulating platelet counts after treatment with ZDV, including a small prospective placebo-controlled trial.[31-36] In patients who respond, platelet counts usually begin to increase within the first week and often rise to more than 100,000/mm^3 by the end of the first month. The reason for the increase in platelet counts seen in patients on ZDV is not clear, but several mechanisms have been proposed. These mechanisms include inhibition of the reticuloendothelial system, stimulation of platelet production in the bone marrow, decreases in virus load, and/or suppression of autoantibody formation. Data is lacking on how long ZDV should be continued if a response occurs, but a recent study suggests that bone marrow suppression may limit the benefit of treatment over time.[36] Although not currently approved by the FDA for this use, there are fewer theoretical risks for an individual taking ZDV as compared to steroids. Therefore ZDV is recommended to our patients initially, with steroids reserved for those who do not want, cannot tolerate, or do not respond to ZDV.

Patients with clinical signs and symptoms of bleeding are treated with platelet transfusions and IVIG (0.4 to 2.0 g/kg/day). Strong consideration is given to starting ZDV and/or steroids. If the bleeding stops, patients are treated as described above, depending on whether their platelet counts are greater than or less than 20,000/mm^3. Splenectomy is reserved for those patients who continue to bleed or have a platelet count of less than 20,000/mm^3 despite medical management. In addition patients whose platelet counts fall to less than 20,000/mm^3 when weaned off steroids are, in our view, candidates for splenectomy. This approach avoids the problems of long-term steroid use.

Candidates for splenectomy should be given intravenous immunoglobulin (IVIG) in the 48 hours preceding splenectomy in a dose of 0.4 to 2.0 g/kg/day. Rapid transient elevations in the platelet count usually occur and frequently obviate the need for platelet transfusions during surgery. The value of the pneumococcal vaccine has not been determined in patients infected with HIV-1 and some evidence suggests that these individuals may have poor immunologic responses to it.[37] However we routinely administer the pneumococcal vaccine before operation, preferably at least 1 week before surgery.[38] We do not routinely prescribe prophylactic penicillin after operation. In patients who fail to respond to splenectomy, steroids, danazol, and/or ZDV are considered.

There is concern about the role of splenectomy in accelerating the progression of HIV-1 infection to AIDS. One report,[39] which reviewed four published series,[4,5,14,19] concluded that patients who underwent splenectomy were more likely to progress to AIDS than were patients who received steroids. The number of patients in this cohort was small, the duration of follow-up was not stated, and the study had no controls. In contrast a study of 45 patients with HAT in France, 17 of whom underwent splenectomy, showed no increase in the risk of disease progression after 22 months of follow-up in the patients who had surgery.[40] In our cohort two symptomatic patients have had their HIV-1 disease progress, but the five asymptomatic patients have remained stable with no change in their clinical status, CD4/CD8 lymphocyte ratios, or absolute CD4 cell counts. We are following this group to determine the long-term effects of splenectomy on the course of HIV-1 infection. Although splenectomy for HAT is a well-tolerated procedure, long-term follow-up of our patients suggests that complete responses are uncommon. These findings, along with the emerging evidence demonstrating ZDV's efficacy in raising platelet counts, support our contention that splenectomy should be reserved for medically refractory HAT.

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Emergency Endotracheal Intubation in Pediatric Trauma

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The purpose of this study was to determine the effectiveness and associated problems of emergency intubation in 605 injured infants and children admitted to the Children's Hospital of Pittsburgh in 1987. We identified 63 patients (10.4%) undergoing endotracheal intubation at the scene of injury, at a referring hospital or in our emergency department. Injuries were to the head (90.5%), abdomen (12.7%), face (11.1%), chest (6.3%), neck (3.2%); or were orthopedic (19%) or multiple (39.7%). Indications for intubation included coma (74.6%), shock (28.6%), apnea (22.2%), and airway obstruction (3.2%). Of 16 complications (25.4%), 13 were immediately life threatening: right mainstem intubation (5), massive barotrauma (2), failure of adequate preoxygenation (2), esophageal intubation (1), attempt at nasotracheal intubation in an open facial fracture (1), and extubation during transport (1). Three were late complications: vocal cord paresis (2) and subglottic stenosis (1). Airway complications led to PO2 < 90 mm Hg in 7 of 12 on first ABG, compared to 9 of 44 in uncomplicated cases ($p < 0.05$). Intubation attempts at the scene of injury were more often multiple, unsuccessful, and associated with airway complications. All four complication-associated fatalities were life-threatening scene complications. Nearly one half (44.4%, 28 of 63) had one of the following problems in respiratory management: major airway complication, PaO2 less than 90, or PaCO2 greater than 45 on either the first or second ABG after arrival at our emergency department. Head injury with coma is the most common setting for emergency intubation. Airway complications are common, and are more frequent in treatment attempt at the scene. Despite endotracheal intubation, injured children in our series remain at high risk for hypoxemia, elevated arterial PCO2, and major airway complications, all of which contribute to secondary brain injury.

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AN OPEN AIRWAY and adequate gas exchange are the central goals of trauma care. With the recognition and treatment of shock, they form the now-familiar mnemonic "ABC" (*a*irway, *b*reathing, and *c*irculation) that summarizes the basic priorities of injury management. Current guidelines for trauma care emphasize an aggressive approach to airway management.[1] Early endotracheal intubation is lifesaving in injuries that cause airway obstruction and allows assisted ventilation of the patient in apnea. Many authorities also recommend that patients with severe head injuries undergo early endotracheal intubation.[1,2] Airway obstruction, aspiration, and apnea are among the major hazards to respiratory function in the brain-injured patient. These factors increase the risk of hypoxemia and thus may result in ischemic brain damage, termed secondary injury, that adds to damage already suffered from the initial injury. Injury-induced brain swelling increases intracranial pressure and compromises cerebral perfusion, representing another cause of secondary brain injury. Endotracheal intubation assures optimal gas exchange and allows controlled hyperventilation to decrease intracranial pressure through cerebral vasoconstriction.[2,3]

Despite these compelling arguments that favor early endotracheal intubation under certain critical circumstances, the efficacy of early airway management protocols are unknown. Airway management in children is a particularly difficult task.[1] We therefore reviewed all cases of emergency endotracheal intubation in children admitted to a level I pediatric trauma center during a recent 12-month period.

Materials and Methods

A comprehensive trauma registry records relevant clinical data from all children with significant injuries requiring hospitalization at the Children's Hospital of Pitts-

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burgh. The trauma service registrar and clinical coordinators collect data concurrently with the child's admission, with the intent to insure complete and accurate capture of all patients and information. Source materials for the registry include prehospital trip records (trip sheets), trauma flow sheets in the emergency room and critical care areas of the hospital, progress notes, laboratory and radiology reports, and other material collected on the child's impatient record. All information are entered on a computer with standard database software.

The data contained on the registry allowed the identification of all acutely injured children who underwent emergency intubation during the 1987 calendar year. The following criteria defined emergency intubation: (1) arrival with an endotracheal tube in place after transfer from the scene of the injury; (2) arrival with an endotracheal tube placed at a referring hospital within 12 hours of transfer to our trauma service; and (3) endotracheal intubation in the Children's Hospital of Pittsburgh emergency department (ED).

The trauma service coordinators and physicians identified all deaths and complications during 1987 using a system of review described at length elsewhere.[4] In brief, a prehospital coordinator (an experienced paramedic) and a trauma nurse coordinator identify prehospital and in-hospital complications on all admitted patients on the basis of their experience and trauma service treatment guidelines. We use a system of audit screens to spot undesired occurances, such as an unexpected return to the operating room or intensive care unit. Attending physicians on the trauma service identify problem cases for review on a weekly basis. These procedures to maximize capture of all trauma service deaths and complications for quality review pinpoint cases that posed difficulties in initial airway management.

The first arterial blood gas (ABG) measurements after arrival in our ED determined the efficacy of airway management. For patients arriving with an endotracheal tube in place, we recorded the initial ABG after arrival; for those intubated in our ED, the first ABG obtained after endotracheal intubation was recorded. Many patients had a second ABG in the ED. We reasoned that procedures for airway control should provide a PaO2 that was sufficiently high to provide a margin of safety should untoward events occur without warning. Therefore we chose values of less than 90 mm Hg to represent suboptimal oxygenation in the absence of chest injuries. In addition, because so many of our patients had head injuries, we believed that inadequate ventilation, PaCO2 greater than 45 mm Hg, represented deficient care. We also noted cases characterized by extreme hyperventilation to PaCO2 $\leq$ 25 mm Hg, because of experimental evidence that cerebral ischemia may complicate hypocarbia-induced vasoconstriction when these low levels are reached.[3]

We reviewed hospital records of the identified cases to cross-check data yielded by the registry. We used data from the hospital record when discrepancies occurred. During the year we submitted data from the registry and discharge diagnoses to the Pennsylvania Trauma Systems Foundation, a nonprofit organization responsible for overseeing trauma care in the state. A private firm, Tri-Analytics, Inc. (Rockville MD), coordinated a statewide registry for the Foundation, including computation of the Glasgow Coma Score (GCS), Trauma Score (TS), Abbreviated Injury Score (AIS), and Injury Severity Score (ISS) for each eligible patient with sufficient data. In the few that did not satisfy Foundation inclusion data, we computed GCS and TS using standard procedures,[1,5] and AIS and ISS according to American Association for Automotive Medicine guidelines.[6]

Chi square, Students' t test, and analysis of variance were used for statistical analysis. Yates' correction for chi square analysis was used when degrees of freedom equalled one.

Results

From January 1987 through December 1987, 605 children were admitted to the Children's Hospital of Pittsburgh Trauma Service. Sixty-three patients (10.4%) arrived with an endotracheal tube placed at the scene of injury (9 patients), or at the referring hospital (37 patients), or underwent endotracheal intubation at the Children's Hospital emergency department (17 patients; Table 1). Although children aged 0 to 4 years were intubated more often (28 of 200 patients; 14%) than older children (35 of 405 patients; 8.6%), the difference was not statistically significant. Head injuries were present in all but 5 of the 63 patients (Table 2), and coma was present in nearly three fourths of patients (Table 3). Of the 16 patients with apnea or airway obstruction, 15 were in coma because of head injuries.

TABLE 1. *Patients Undergoing Endotracheal Intubation at the Scene, at the Referring Hospital, or on Admission to the Emergency Room*

	Intubation		Tracheotomy or Needle
Location (N = 63)	Successful	Unsuccessful	Cricothyroidotomy
At scene (9)	8	6*	2
Referring hospital (37)	36	0	1
Children's Hospital (17)	17	0	0

* Of the unsuccessful scene intubations, 3 were successfully intubated at Children's Hospital, 1 was intubated at the referring hospital, and 2 underwent attempts at cricothyroidotomy. One patient with an unsuccessful cricothyroidotomy later underwent successful intubation at the referring hospital. No adequate airway control was possible in the second unsuccessful cricothyroidotomy, which is included in the total of nine scene intubations.

TABLE 2. *Body Region Injured*

Region	N = 63*	%
Head	57	90.4
Neck	2	3.2
Chest	4	6.3
Abdomen	8	12.7
Orthopedic	12	19.0
Facial	7	11.1

* More than one body region was injured in 25 patients (39.7%).

When scene intubations were successful, they more frequently required more than one attempt (6 of 8 cases, $p < 0.05$), compared to those done at the referring hospital (5 of 37 cases) and in our ED (4 of 17 cases). The only unsuccessful attempts at intubation were at the scene of injury, where prehospital personnel were unable to place ETT in 6 of 14 (42.8%) children (Table 1). Of these six, three were subsequently intubated at Children's Hospital and one at the referring hospital. Two others underwent unsuccessful attempts at needle cricothyroidotomy. Both suffered barotrauma with massive subcutaneous emphysema. One of the two, a 14-year-old boy, was later orally intubated at the referring institution before transfer, but he later died of head injuries. The second, an 11-year-old boy, also with head injuries, died during transfer from the scene without adequate airway control.

Airway-related complications occurred in 16 patients (6 scene, 6 referring hospital, and 4 Children's Hospital; 25.4%), summarized in Table 4. Thirteen were immediately life threatening: right mainstem intubation (5), massive barotrauma (2), failure of adequate preoxygenation (2), massive aspiration(1), esophageal intubation (1), attempt at nasotracheal intubation in an open facial fracture (1), and extubation during transport (1). Three were late complications: vocal cord paresis (2) and subglottic stenosis (1).

FIO2, recorded in 35 cases, was 1.0 in 24 (68.8%), 0.8 in 1; 0.5 in 5; and less than 0.4 in 5. The 28 without a recorded FIO2 were ventilated by a bag apparatus supplied by an oxygen tank or a wall oxygen source, and no FIO2 was specifically recorded. In two patients, however, the wall source was not turned on so that the child received room air during bag and mask ventilation that preceded intubation. We considered these airway management complications, even though arterial oxygen levels were 122 and 313 mm Hg on the first ABG after intubation.

TABLE 3. *Associated Conditions*

Condition	N = 63*	%
Coma/unstable neurologic	47	74.6
Shock	18	28.6
Apnea	14	22.2
Airway obstruction	2	3.2
Other	2	3.2
Stable	8	12.7

* More than one condition was present in 19 patients (30.2%).

Table 5 summarizes the incidence of suboptimal oxygenation (PaO2 < 90 mm Hg), hypercarbia (PaCO2 > 45 mm Hg), and extreme hypocarbia (PaCO2 < 25) in 56 cases (four with chest injuries are listed separately, and no ABGs were obtained in three fatalities). Because our goal of oxygen administration is to provide a margin of safety in addition to adequate oxygenation, we decided that airway procedures that did not provide PaO2 ≥ 90 mm Hg represented suboptimal oxygenation. One in four had a PaO2 less than 90 mm Hg, with significantly more cases with airway complications having low PaO2 than noncomplicated cases ($p < 0.05$). Suboptimal oxygenation occurred more frequently in fatalities and children with apnea but failed to reach statistical significance. Site of intubation (Children's Hospital, transferring hospital, or scene of injury) and age did not significantly influence the occurrance of suboptimal oxygenation or hypercarbia. Hypoventilation (PaCO2 > 45) occurred in four children (7.1%). Extreme hyperventilation (PaCO2 < 25) was present in 39.3% (15 of 56 cases).

Fifteen children died (23.8%). One died from uncontrolled hemorrhage from avulsion of the hepatic veins. Fourteen died with head injuries, of which three suffered gunshot wounds to the head. The other 11 deaths involved major head injuries with AIS of 3 to 6. Nine of the eleven had no other injuries. One of the two remaining fatalities also had a small bowel laceration and the other had an acetabular fracture. The four deaths involving scene intubations were complicated in each case by a major airway mishap (Table 4). Deaths were not associated with age or site of intubation. Deaths were associated with a higher ISS and Head AIS, as expected (Table 6).

Airway complications, hypoxemia, and hypercarbia reflect difficulties in respiratory management and are summarized in Table 6. At least one of these factors was present in 44.4% of cases (28 of 63 cases) and were significantly more common in scene intubations (77.8%; 7 of 9 cases). Table 7 attempts to show the possible effect of secondary injury due to respiratory management problems (*i.e.*, airway complications, hypoxemia, and hypercarbia) on mortality for head injuries of an equivalent AIS level. No statistically significant differences were found between the mortality rates among children who experienced airway or respiratory difficulties and those free from airway complications when stratified for AIS. However, cases with an airway complication, PaO2 less than 90, or PaCO2 more than 45 had a mortality rate more than twice that of cases free from respiratory problems ($p < 0.05$).

TABLE 4. *Airway Complications in Pediatric Trauma*

Complication	Number	Site*	Age (Years)	Death(s)
Right mainstem intubation	5	1S, 3R, 1C	1, 4, 4, 7, 8	0
Massive subcutaneous emphysema from cricothyroidotomy needle	2	2S	12, 15	2
Esophageal intubation	1	S	1.5 months	1
Failed nasotracheal intubation in a open LeFort III	1	S	4.5	1
Massive aspiration	1	R	15	0
Bilateral vocal cord paralysis	1	R	6	0
Subglottic stenosis	1	R	4	0
Failure of adequate preoxygenation	2	2C	4, 10	0
Extubation during transport	1	S	8	0
Left vocal cord paralysis	1	C	5 months	0
Total	16	6S, 6R, 4C	mean 6.45	4

* Site refers to where the child was intubated: S, scene of injury; R, referring hospital; C, Children's Hospital.

We defined unnecessary intubations as those occurring in survivors who did not have apnea or airway obstruction, had a GCS of more than 10, and were intubated for less than two days. Of our study group, 30.2% (19 of 63 cases) satisfied these criteria. All but one had head injuries. Mean GCS was 14.5, with a range of 10 to 15. Scene personnel intubated 2; referring hospital physicians, 13; and Children's Hospital physicians, 4. Eighteen had ABG determinations, which are summarized in Table 5. Of note is that 26.3% (5 of 19 cases) had PaO2 less than 90 mm Hg. Six of the 19 (31.6%) suffered airway complications (3 right mainstem intubations, 2 cases of vocal cord paralysis, and 1 massive aspiration).

TABLE 5. *Arterial Blood Gas Measurements in Injured Children Undergoing Endotracheal Intubation (Excluding Chest Injuries)*

		PaO2	PaCO2	PaCO2
Category	N	<90	>45	<25
Total	56	16 (29)	4 (7)	22 (39)
Site of intubation				
Children's Hospital	16	2 (13)	0 (0)	6 (38)
Transfer Hospital	32	10 (31)	3 (9)	15 (47)
Scene	8	4 (50)	1 (13)	1 (13)
Age				
Less than 1 year	10	1 (10)	1 (10)	5 (50)
1 to 4 years	16	5 (31)	1 (6)	5 (25)
5 to 9 years	18	5 (28)	1 (6)	8 (39)
10 to 19 years	12	5 (42)	1 (8)	4 (33)
Airway complication				
Present	12	7 (58)*	2 (17)	1 (8)
Absent	44	9 (20)	2 (5)	21 (48)
Deaths				
Fatalities	13	6 (46)	2 (15)	5 (38)
Survivors	43	10 (23)	2 (5)	17 (40)
Apnea				
Present	13	5 (38)	1 (8)	6 (46)
Absent	43	11 (26)	3 (7)	16 (37)
Chest injury	4	2	0	2
Unnecessary intubations	19	5 (26)	1 (6)	6 (33)

Total excludes four children with chest injuries and three who did not have arterial blood gas measurements (two fatal cases and one survivor intubated because of apnea). Unnecessary intubations are described as those occurring in surviving patients without apnea or airway obstruction, who have a GCS of more than 8, and remained intubated for less than two days.

$p < 0.05$ by chi square test.

* Percentages are shown in parentheses.

Discussion

Timely endotracheal intubation is among the basic interventions in trauma care that provide a therapeutic margin that may ensure survival under critical circumstances. Although its role in the management of apnea and the obstructed airway is obvious, the most frequent indication for endotracheal intubation in our series was in the management of head injury. Ninety per cent had head injuries and three fourths were in coma. Of the 25% noted to be in apnea or to have an obstructed airway, all but one had a coexisting head injury.

The rationale for endotracheal intubation in the management of the head-injured patient, outlined above, justifies current recommendations for early endotracheal intubation and assisted ventilation.[1,7,8] Achieving these goals in children is difficult. In our study we encountered major airway complications with disturbing frequency in nearly one fourth of intubated injured patients. Two thirds of patients intubated at the scene of injury experienced major complications. All four complication-related deaths occurred during scene intubation attempts. We judged that more than 80% (13 of 16) of complications were life threatening, requiring immediate corrective action to avoid death or severe hypoxia.

It is not surprising that airway complications were associated with ABG with low PaO2 (< 90 mm Hg; 58%, 7 of 12 cases). But we still encountered suboptimal ABG (defined as PaO2 < 90 and PaCO2 > 45) in noncomplicated cases. In all an airway complication or suboptimal ABG was present in 44.4% of cases (28 of 63; Table 6). Despite endotracheal intubation, head-injured children remain at considerable risk for secondary brain injury from hypoxia and intracranial hypertension.

TABLE 6. *Deaths, Airway Complications, Arterial Blood Gas (ABG) Results in Relation to Survival, Site of Intubation, Head Abbreviated Injury Score (AIS), and Injury Severity Score (ISS)*

Factor	N	ISS (Mean ± S.D.)	Head AIS ≥ 4 (%)	Deaths (%)	Compl't'ns (%)	Initial ABG		Second ABG		Complication Lo PO2 or Hi PCO2
						Lo PO2	Hi PCO2	Lo PO2	Hi PCO2	
Total	63	20.7 ± 16.5	44 (69.8)	15 (23.8)	16 (25.4)	16	4	3	4	28 (44.4)
Survival										
Death	15	32.4 ± 22.7*	12 (80.0)*	—	4 (26.7)	6	2	2	2	10 (66.7)
Alive	48	17.0 ± 12.2	22 (45.8)	—	11 (22.9)	10	2	1	2	18 (37.5)
Site of Intubation										
CHP	17	17.6 ± 7.5	10 (58.8)	3 (17.6)	4 (23.5)	2	0	0	1	7 (41.2)
Refer	37	20.0 ± 18.8	17 (45.9)	8 (21.6)	6 (16.2)	10	3	2	1	14 (37.8)
Scene	9	29.3 ± 18.2	7 (77.8)	4 (44.4)	6 (66.7)*	4	1	1	2	7 (77.8)†
Head AIS (N = 56)										
≥4	34	27.9 ± 18.3*	—	12 (35.3)†	10 (29.4)	8	3	1	4	17 (50.0)
<4	22	12.0 ± 8.2	—	2 (9.1)	5 (22.7)	7	1	2	0	9 (40.1)
ISS										
≥10	44	—	34 (77.3)*	14 (31.8)*	12 (27.3)	12	3	1	4	21 (47.7)
<10	19	—	0 (0.0)	1 (5.3)	4 (21.0)	4	1	2	0	7 (36.8)
Complication, lo PO2 or hi PCO2										
Present	28	24.3 ± 17.1	17 (60.7)	9 (33.3)	—	—	—	—	—	—
Absent	35	17.9 ± 15.9	18 (50.0)	6 (16.7)	—	—	—	—	—	—

Head AIS includes only the 56 head-injured patients. All ABG are in mmHg. "Lo PO2" indicates PaO2 < 90; "hi PCO2" indicates PaCO2 > 45.

* $p \le 0.05$.
† $p = 0.06$.

Although we could not find a significantly higher mortality rate with airway or gas exchange difficulties for a given degree of head injury severity (Table 7), other authors have found that airway and respiratory problems have an adverse effect on head injury. Gentleman and Jennett[9] found that many head-injured patients suffer from inadequate respiratory management. Of 150 patients (21% were children), 40 (27%) had evidence of airway obstruction. Eighteen progressed to respiratory arrest, and 34 (23%) had documented hypoxemia. Only 28% of their patients had an endotracheal tube in place, 44% had an oral airway, and 28% had neither. The authors found a higher mortality rate among those who suffered hypoxia, hypotension, or both, than among those who did not have those complications. Their findings substantiated the secondary injury effect of airway-related and circulatory complications in head injury.

The high death rate (23.8%) may be a reflection of the severity of injury and extremity of conditions in these children. Mean ISS among all patients was 20.7, reflecting serious multisystem injuries. But the severity of injury did not fully explain the high frequency of airway difficulties. The mean ISSs of scene-intubated and complicated groups were high (Table 6), but differences did not reach statistical significance. When patients with high ISSs (≥ 10) were compared to those with low ISSs (< 10), complication rates and suboptimal ABGs were not statistically different.

Scene intubation proved to be difficult, reflected by the high proportion that required multiple attempts before successful intubation and the number of failures. Two attempts at cricothyroidotomy ended in disaster. This reflects the confusion that surrounds the scene of injury, which includes environmental conditions, inadequate light, limited personnel, and a multitude of distracting influences. What may be an easy airway in the operating room may be an impossible one in the field. Still, complications occurred at the referring hospital and our ED where conditions are more favorable to successful airway control.

Gauging the depth and rate of assisted breaths in small subjects to achieve recommended PaCO2 levels of 25 to 30[2] is difficult until ABGs are obtained. We encountered both hypo- and hyperventilation, although the latter was more common. We found that one in four (27%, 15 of 56 cases) had PaCO2 less than 20, levels that in theory risk cerebral ischemia from excessive hypocarbia-induced

TABLE 7. *Head AIS, Respiratory Difficulty, and Mortality Rates in 56 Children with Head Injuries*

AIS	Airway Complication, Lo PO2 or Hi PCO2	N	Survived	Died
1–2	Yes	1	1	0
	No	5	5	0
3	Yes	8	6	2
	No	8	8	0
4	Yes	10	7	3
	No	13	10	3
5–6	Yes	7	3	4
	No	4	2	2
Total	Yes	26	17	9 (34.6%)*
	No	30	25	5 (16.7%)

One child with head injury did not have a defined Abbreviated Injury Score (AIS). Lo PO2 indicates PaO2 < 90; hi PCO2 indicates PaCO2 > 45.

* $p < 0.05$.

cerebral vasoconstriction.[3] We expected that problems in ventilation would be a particular problem in the very young, and in community hospitals not experienced in pediatric-assisted ventilation. This was not the case, because unacceptable PaCO2 values were encountered in all age groups and within all settings.

A troubling group is the 19 surviving patients who arrived with relatively high GCSs (≥ 10) and were extubated soon after admission (within two days), indicating that endotracheal intubation and assisted ventilation were not necessary. Nearly one third suffered airway complications and more than one fourth (Table 5) had PaO2 less than 90. Because the risks of pediatric intubation are considerable, the clinical challenge is to identify those children who will not require intubation. None of the 19 had airway obstruction, all were breathing spontaneously, and none were in deep coma (GCSs in all were 10 to 15, with a mean of 14.5). Thus it appears that injured children who are breathing and who have GCSs ≥ 10 require only supplemental oxygen and simple manual maneuvers to keep an open airway (such as a chin-lift or jaw-thrust maneuver), unless neurologic or respiratory deterioration occurs. The data suggests that these patients can be identified and spared the risks of emergency intubation in the field or before transfer. Should airway control be necessary for computed tomography (CT) or surgery, the procedure can be performed at the trauma center where the procedures will take place, avoiding the hazards associated with interhospital transfer. Patients in coma will require airway control before transfer.

Our study may suffer selection bias from the transfer of patients presenting with difficult management problems: very young patients; those with severe head trauma; and those with difficult airway problems. This is reflected in our data: more of our patients who were less than 4 years of age arrived intubated; head injuries were present in nearly all patients reviewed; and the frequent occurrence of life-threatening airway problems.

Our findings underscore the necessity of education and training of those who care for acutely injured children in the field, in community hospitals, and in pediatric trauma centers. They confirm the difficulties in pediatric airway management that arise from the unique anatomic features of the pediatric airway, and inexperience in technique that arises from lack of exposure and practice.

Airway management is a difficult skill. De la Roche[10] documented the difficulties in achieving adequate ventilation in adult-sized mannequins among trainees. Pepe, Stewart, and Copass,[7] recognizing these problems, suggest that a small but completely trained cadre of life support specialists handle the bulk of emergency and trauma care that require advanced resuscitative skills, such as endotracheal intubation. However, Tsai and coworkers[11] in Fresno County, California, note that the opportunity to attain and maintain proficient pediatric emergency skills is limited. Children accounted for only 10% of all ambulance runs, although they comprise 32% of the population; none underwent endotracheal intubation during the 12 months of review. Pediatric emergencies comprised only 5% of the prehospital emergency caseload in Jerusalem, and only 2.6% of children (8 of 307) received endotracheal intubation in 18 months.[12]

Although none can argue that endotracheal intubation is the technique of choice for airway management in the obstructed or apneic patient,[1,7,8,13] there are few studies that document the effectiveness of advanced life support techniques, including endotracheal intubation, in the prehospital treatment of trauma. Jacobs and Sinclair[8] documented that resuscitative techniques in the field improved TS in patients with an initial TS of 4 to 13. However, only the most severely injured patients with TS 1 to 3 failed to show an improvement in TS, and were the only ones to undergo endotracheal intubation. Their status may have been so compromised that improvement in response to any therapeutic measure may have been impossible.

Airway control and endotracheal intubation are difficult tasks in pediatric trauma. Complications and inadequate gas exchange are unfortunately common, even with an endotracheal tube in place, and put the child at risk for secondary cerebral injury from hypoxemia and intracranial hypertension. Indications for emergency endotracheal intubation require careful review, particularly in children with head injury who are breathing without obstruction.

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The Amazing Adventures of Wilburt C. Davison, Wilder G. Penfield, and Emile F. Holman While Rhodes Scholars in Medicine at Oxford During World War I, 1913–1917

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WILBURT CORNELL DAVISON, founder and first Dean of the Duke University Medical School; Wilder Graves Penfield, noted neurosurgeon, founder and first Director of the Montreal Neurological Institute of McGill University; and Emile Frederic Holman, noted vascular surgeon and long-time chairman of the Department of Surgery at Stanford University, were Rhodes Scholars and medical students together at Oxford during the early years of World War I (Fig. 1). Probably few, if any, students since have had such exciting adventures or been so actively involved while in medical school in so many of the major historical events of their time.

Before entering Oxford, Davison and Penfield had been classmates at Princeton, from which they received their undergraduate degrees in 1913. Holman had graduated from Stanford in 1911 then worked for 2 years as a secretary to Stanford president David Starr Jordon, famous naturalist, fervent pacifist, and one of the more noted and peripatetic lecturers of the time.

As undergraduates, all three had hoped to study medicine and had long held aspirations of winning one of the new Rhodes Scholarships that had been established just a few years before. In those days, the 3-year Rhodes Scholarship with its $1500 annual stipend would nearly cover the cost of a medical education.

Davison won his Rhodes scholarship in 1912 and entered Oxford's Merton College for the fall term in 1913. Holman won his scholarship in 1914 and entered Oxford's St. John's College that October.

With the outbreak of war in August 1914, Penfield, fearing that the war would disrupt all teaching at Oxford, at first abandoned his newly won Rhodes scholarship for which he had worked so hard. After coaching the Princeton varsity football team that fall, Penfield enrolled, instead, in Columbia University's College of Physicians and Surgeons. In December, however, he recieved a postcard from Davison[2] reassuring him that the teaching at Oxford with fewer students because of the war was, if anything, better than ever. Davison's card was persuasive, for Penfield immediately arranged for the reinstatement of his scholarship and sailed for England. He entered Oxford's Merton College in January 1915 in time for the winter term.

The first of Holman's student adventures began while enroute to Oxford. By early 1914 there was growing concern that guerrilla wars, border clashes, and uprisings in some of the countries of southeastern Europe might set off a larger war.

In late spring 1914, David Starr Jordon decided to make a personal peace crusade through the Balkans, Greece, and Turkey to preach the evils of war. He invited Holman, then his secretary, to accompany him. Holman gladly accepted because their itinerary was to end in London in time for him to enter Oxford for the fall term.

The trip took them through rugged Balkan back-country and among warring guerrilla groups where travel was frequently hazardous. When they left Sofia, Bulgaria, the Queen loaned them her open touring car and two armed soldiers to protect them. Frequently they found themselves living under primitive conditions with no, or appalling, sanitary facilities. At the Greek Macedonian border, they were placed in custody of a Greek army unit with whom they traveled for a time. The only food was served from a common bowl into which each person dipped his own spoon. Eventually Jordon developed dysentery. In spite of it, and his age, then 63, he pressed on with his peace campaign. Holman, however, soon became skeptical of success for Jordon's crusade for, as he wrote to a friend, "It seems we no longer leave a country when they go to war."[3]

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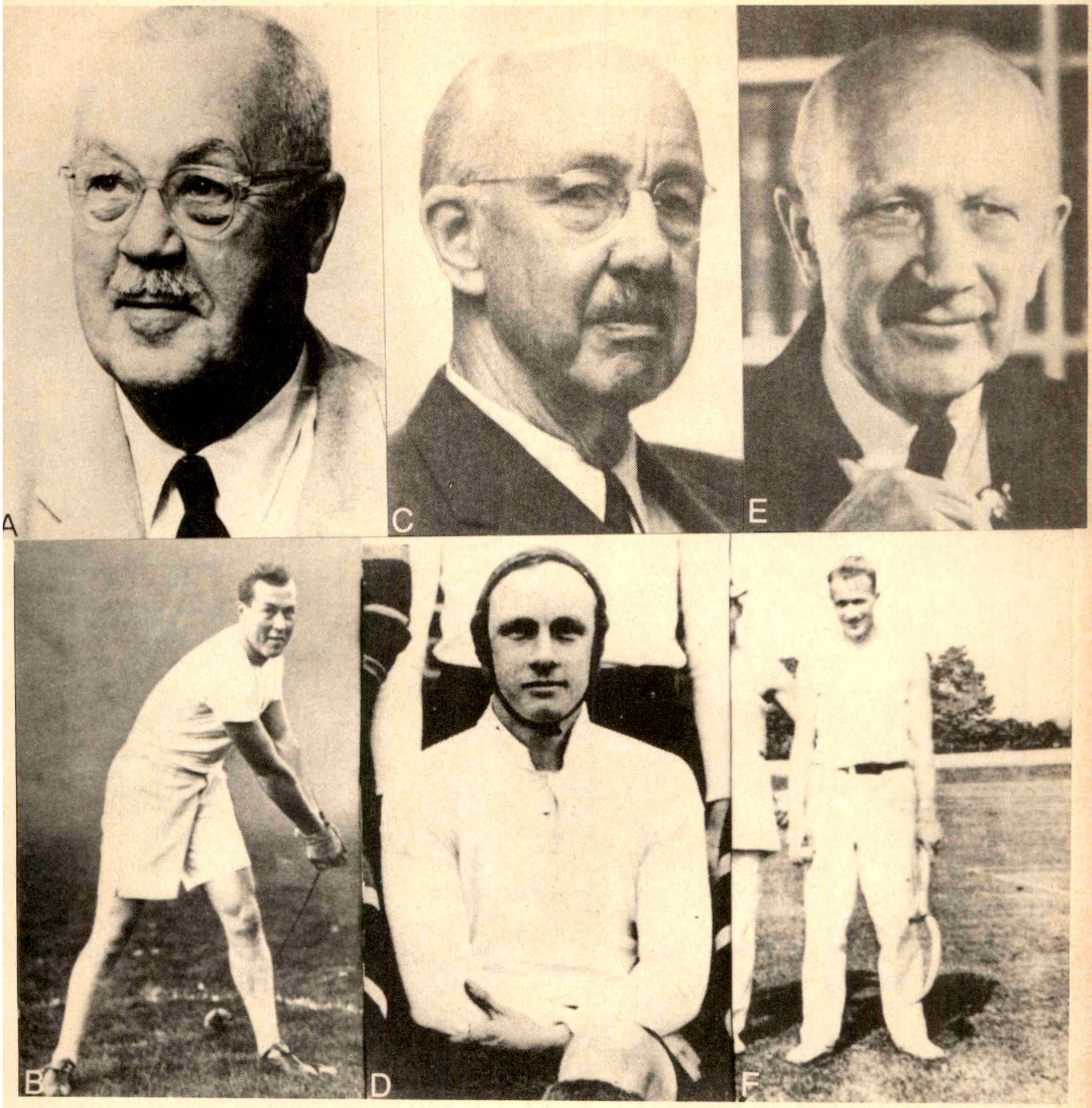

FIGS. 1A–F. (A) Dr. Wilburt C. Davison in his later years. (B) he is shown throwing the hammer at Oxford. He was also on the water polo team and rowed for the Oxford "torpids" or second boat. (Courtesy of Davison Archives, Duke University Medical Center) (C) Dr. Emile F. Holman in his later years. (D) At Oxford in his rugby football uniform. In 1971, when this photograph of Holman in his rugby uniform appeared in the Stanford Alumni Almanac, he wrote the editor:[1] "My academic friends will be surprised to note that I played rugby football against Cambridge, a phenomenon that was possible only in a wartime England." (Courtesy of Stanford Alumni Almanac) (E) Dr. Wilder G. Penfield in his later years. (F) In tennis garb at Oxford. Penfield had been a football star at Princeton and greatly enjoyed playing rugby football at Oxford. (Courtesy Penfield archives, Osler library, McGill and Davison archives, Duke University.)

Finally Jordon was so ill on the last leg of their journey that Holman, now playing the role of nurse, began to despair whether Jordon would survive long enough to reach proper medical care. As Holman described it,[3] "We arrived in Brendisi aboard a Russian ship and caught a train for Naples. By this time, Dr. Jordon was lying in the aisle as he was too sick to sit. His clothes were in disarray and he had a large sloppy hat balancing on one ear. We arrived about midnight and when we reached our hotel, the clerk, first refused us rooms stating 'he didn't take in drunks.'"

Next day Jordon was hospitalized and fortunately recovered. Jordon next extended his peace crusade to the feuding Catholics and Protestants in northern Ireland. However the futility of Jordon's peace efforts soon became evident when World War I broke out shortly after he and Holman returned to London.

In the meantime, Davison, having finished his first year at Oxford, had spent his summer vacation in Europe traveling with his fiance Atala Scudder and her family. Soon after war was declared, the Germans made their rapid advance nearly to Paris and Davison and the Scudders had a hectic time escaping the war zone. With other fleeing American tourists they were finally evacuated from Le Havre back to England aboard the U.S. Cruiser Tennessee.

Some of the other American Rhodes Scholars the war caught vacationing on the continent were less fortunate. Davison, describing some of their experiences in a letter to his father, wrote:[4]

> Herman Bruckholtz, Rhodes scholar from Minnesota and his brother were staying in Nuremburg and, when the army (German) mobilized, they seized them for Germans for their names were distinctly Teutonic and they spoke the language unnecessarily well. They were being marched toward the Russian front when they broke ranks and rushed into an American consulate, where during the battle royal that followed they finally proved their identity and were released.
>
> P. H. Brodie, Rhodes scholar from Arkansas, was arrested in Heidelberg and led through the streets like a Roman captive with a howling mob at his heels. He had tried to mail a letter at the post office after it had closed and in his efforts to find the letter box, he had walked around to the back entrance to the building which was in a dark alley. The police thought they had caught a Russian spy in the act of blowing up the post office. He was released after some difficulty.

By October 1914, when Davison returned to Merton for his second year and Holman entered St. John's College for his first term, the whole atmosphere at Oxford had changed. There had been a mass exodus of the British students into the armed forces. The quads and eating halls were largely deserted. About the only students remaining were the physically unfit or those from neutral countries. In the medical school class with Holman and Penfield there were only seven other students.

All three American students became favorites of Sir William Osler, the Regius Professor of Medicine and the most dominant figure in the school. They were also to be Osler's last American students. Davison and Penfield were especially close to the Oslers and were frequent guests for tea and dinner at "The Open Arms," as the Osler home was affectionately known.

All three were also close to Sir Charles Sherrington, noted head of the physiology department (Fig. 2) and later Noble Laureate. Sherrington had such high regard for their work as students that as late as 1929 he was still using data from their student experiments to illustrate his book of Mammalien Physiology.[5]

Being so close to the war, and with all able-bodied men in uniform, it is not surprising that these three American scholars were self-conscious of their civilian status. Undoubtedly this enhanced their eagerness to spend their vacations in some type of war work on the continent.

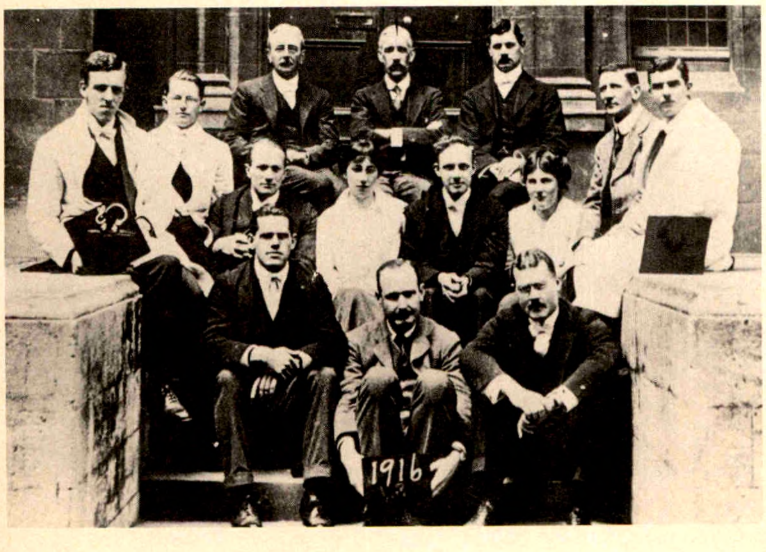

FIG. 2. The Oxford University Physiology Department examination day in 1916. Top row left, Professor Sherrington. Top row center, Sir F. Gowland Hopkins, noted biochemistry professor at Cambridge University and guest examiner at Oxford. Top row right, H. M. Vernon, tutor. Penfield is seated on the second row just to the left of the first female student from the left. Holman is seated on the second row between the two women. The latter were the only British students. Davison is in the front row, far right. (Reprinted from *The Persisting Osler: Selected Transactions of the First Ten Years of the American Osler Society* by J. A. Barondess, J. P. McGovern, and C. G. Rowland, eds., p. 185, with permission of Aspen Publishers, c 1985.)

Penfield, however, was warned by Osler that he must use his vacations, at least the first two or three, to take outside additional courses if he wished to finish his preclinical work in 2 years.

Davison, on the other hand, at the beginning of the 6 week winter vacation in December 1914, went to Paris. Equipped with a letter of introduction from Osler, he was taken on as an orderly at the American Red Cross Ambulance War Hospital at Neuilly, France. Because of a shortage of trained personnel, he was soon pressed into service as a wound dresser and anesthetist.

After the Balkan trip and while waiting in London to enter Oxford, Holman, through Dr. Jordon, had become acquainted with Herbert Hoover, a prominent young Stanford alumnus and mining engineer then working in London. By the time Holman was to start his first Oxford vacation 2 months later, Hoover had been made head of the Belgium Relief Commission, and Holman volunteered to work as a temporary supervisor for the Commission in Holland and German-occupied Belgium. His job was to see that the American food shipments through neutral Holland got through into his assigned sector in Belgium and were properly distributed and that the Germans honored their agreement not to seize the supplies for themselves.

Some of the terrible suffering and human misery he encountered during this experience were permanently etched in Holman's memory and were reflected in his letters at the time. In one to Dr. Jordon, he wrote:[6]

> To Cherleroi through several small villages, not a whole house is standing. . . . Each has its little idle group of restless men waiting on the street corner for something to happen that never occurs, each has its bread lines and soup kitchens feeding free of charge 52,000 in Brussels, 35,000 in Antwerp, 30,000 in Liege . . . each has its increasing band of street beggers.
>
> I am reminded frequently of our experiences . . . in the war ridden Balkans . . . the great number of refugees. . . . At first these refugees (Belgian) were quartered in private homes, in empty warehouses, in tents, and even in the windowless and doorless canal and river lighters alongside the docks in Rotterdam and Flushing, men, women and children huddled together in promiscuous misery. As a result, contagious diseases broke out—typhus, scarlet fever, diphtheria and measles.

Near the end of that same vacation period, Davison, working at the ambulance war hospital in France, was about to return to his Oxford classes when he received a letter from Professor Sherrington stating that W. P. Graham, a retired Colonel of the British Army Medical Corp and friend of Sherrington, was organizing a voluntary medical group to go to Serbia to help with the wounded. The letter stated he could arrange a leave of absence for Davison from his Oxford studies if he would like to go. Davison, of course, signed up at once.

The advance party of their group consisted of two doctors and one nurse, with Davison listed as an anesthetist. The voyage out to Salonika was interesting, but the overland trip to Nis, Serbia, was not without its hazards as they traveled by train through the Vardar valley where bands of revolutionary Bulgarians and Macedonian Serbs were fighting.

The Austrian invasion of Serbia in the opening months of World War I had driven the poorly equipped Serbian army and the civilian population southward. The huge number of refugees plus the army caused serious overcrowding of their small southern cities and villages.

Then in November 1914, after receiving supplies and ammunition from France, the Serbian army struck back at the badly overextended Austrians, stopping their advance and capturing some 60,000 Austrian troops. Although this proved a great military victory for the Serbs, the 60,000 Austrian prisoners of war only worsened, for the beginning winter, the terrible overcrowding behind the Serbian lines.

Other than in the larger cities, the housing and sanitation conditions in Serbia, even in peacetime, were extremely poor. Most of the houses were one-story mud wall constructions with dirt floors and no sewers. In the cold weather, without bathing facilities and the crowding of people often 6 or 8 to a small room, vermin flourished.

These were the conditions Davison's small advance party encountered when they arrived in Krusevac near Nis (Fig. 3), the temporary Serbian capital. Davison described the scene as follows:

> Every available room was filled usually by a whole family, and soldiers and prisoners were forced by lack of space to sleep in the railway stations, coffee houses or even in the streets. We were not surprised at the rate at which the filth and vermin had increased. In the railway yard at Nis [Fig. 4], for instance, I had to step carefully across sleeping Austrian prisoners who were huddled together on the ground, some having a burlap bag to cover them, others uncovered and shivering, their overcoats worn through and their feet protruding through their boots making altogether as the night was bitterly cold, a picture of hopeless misery. Practically every known contagious disease seemed to flourish and the hospitals were filled with nearly all varieties from mumps, scarlet fever and diphtheria to typhoid relapsing fever and typhus. This last was the most important and dangerous.

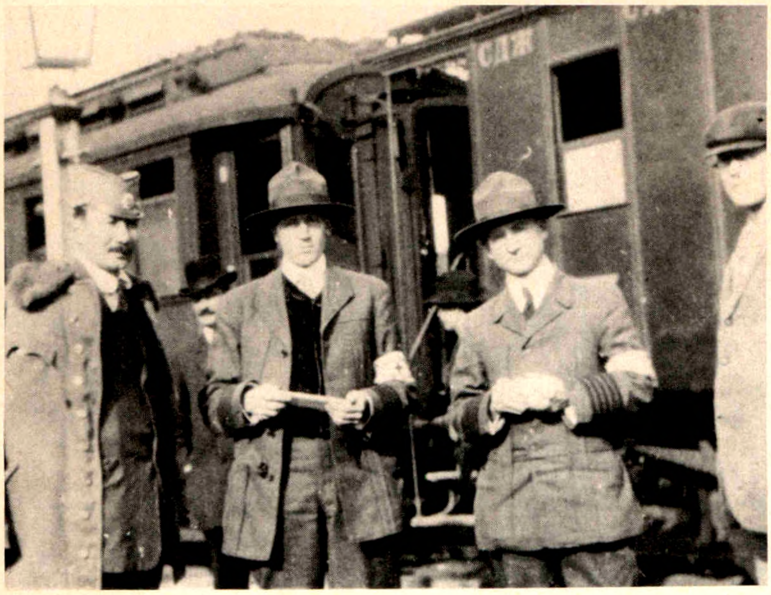

FIG. 3. Medical officers of the advanced party of volunteers to help with the Serbian wounded (in Red Cross uniforms with arm bands) shortly after their arrival in Krusevac, Serbia. Surgeon F. F. Gardner, second from left. Medical student and anesthetist Wilburt Davison (with cap) is shown at far right. A Serbian Army officer is on the far left. At the time of their arrival in Serbia in early February 1915, virtually all fighting had stopped and there were no new wounded to care for. Instead, they found themselves in the midst of a raging typhus epidemic of immense proportions. (Photo courtesy of Davison Archives Duke University Medical Center.)

Instead of being an anesthetist on a surgical team, I became a typhus specialist and looked at rashes, took temperatures and administered aspirin for the terrific headaches of typhus. There was no specific treatment and the patients died like flies. The only thing known about typhus was that it was louse borne.

In the hospitals, conditions were most primitive for except in Belgrade which was a modern city, there was no running water, no lights, no drainage, no sewage, in fact, not a single modern convenience of any kind. Sacks of hay served as mattresses for there were practically no beds to be found. There were no sheets or pillows so cleanliness was only comparative, and it was difficult to prevent the spread of the disease even within the hospital walls.

Among the doctors and nurses the sacrifice of lives has been proportionally heaviest for there seems to be no way to protect the body from the infected lice while passing through the wards. Nurses seemed to suffer worse than doctors from the vermin and disease as their long skirts were constantly brushing against things as they walked. Lady Paget's unit at Skopje wisely adopted harem skirts and others followed their example. Of the Americans (doctors and nurses) serving in Serbia, fourteen had typhus or relapsing fever of which three have died.

The only way to keep free of lice was eternal vigilance and cleanliness. I bought a pig trough in the market. However, trying to bathe with icy water in this hollowed out log which upset at every shiver, was rarely successful.

Picking the cooties whenever they were felt and frequent "seam inspection" of underwear and clothes also were necessary, but one never knew whether the lice which were removed had been on some patient or had become infected.[7–9]*

This Serbian pestilence of 1915 was the worst typhus epidemic of modern times. In less than 6 months it killed 150,000, including 30% of all Serbian physicians.[11]

With the warming of the weather, the epidemic began to wane. Davison's group received word from Paris that the remainder of their unit was not coming, but that an American Red Cross Sanitary Commission with Richard Strong, Hans Zinsser, and Joseph Hopkins was enroute to handle the typhus epidemic. With few, if any, wounded to look after, Davison and one of the unit surgeons, F. F. Gardner, decided to return to England.

When they stopped in Nis, they had a chance encounter in a cafe with Sir Thomas Lipton, the famous tea mogul and yachtsman. Lipton had transported some of the volunteer units to Serbia as far as Salonika on his yacht, *The Erin.* He invited Davison and Gardner to return to England aboard his yacht (Fig. 5). Among Lipton's other passengers, guests were Prince Paul of Serbia, the editor of the *London Daily Mail*, and Dr. Hodge from the American Red Cross Hospital at Gevgelija, Serbia.

Just before sailing Dr. Hodge complained of headache. He was immediately checked for a typhus rash that was present and he was taken ashore to a Greek hospital. Dr. Gardner, the only other physician in the group, volunteered to stay with Hodges, hoping to catch up with *The Erin* perhaps in Italy, for the rest of the voyage to England.

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*A very similar version of Davison's experiences in Serbia and during his return to England via Italy, Austria and Germany appears in *Davison of Duke; His Reminiscences.*[10]

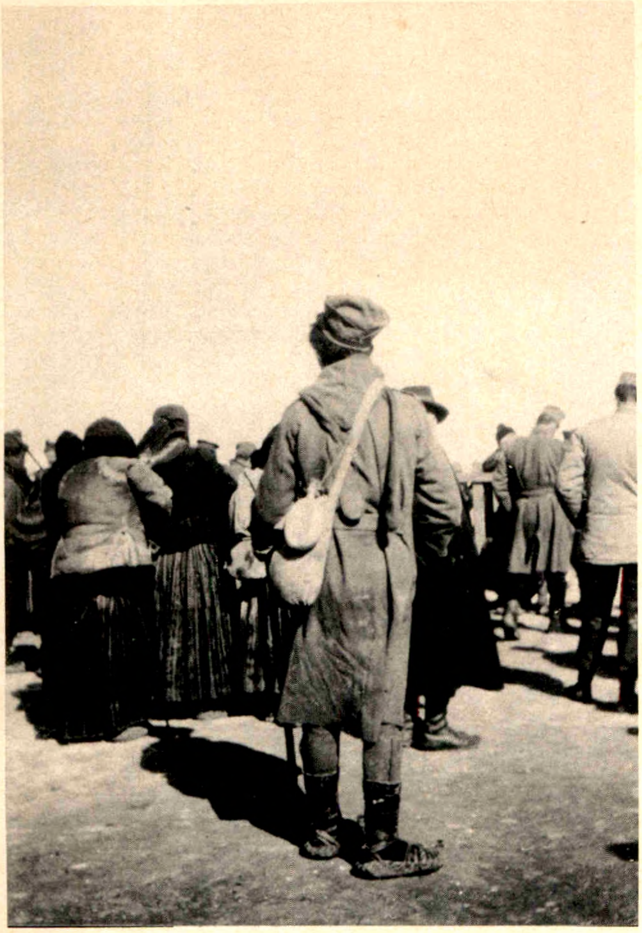

FIG. 4. Crowds of Serbian refugees were everywhere, as were captured Austrian soldiers such as the one shown in the foreground. Note the strapped-on soles on his worn-out boots. These 60,000 Austrian prisoners of war were not closely guarded and could wander about seeking odd jobs and warmer and safer living conditions than in the disease-ridden camps provided for them. The death rate from typhus was highest among the Austrian prisoners. (Photo courtesy of Davison Archives, Duke University Medical Center.)

The editor of the *Daily Mail* was anxious to get first-hand information about wartime conditions in northern Italy and in Austria and Germany. Consequently, when *The Erin* reached Naples, he dared Davison, the only one on board from a neutral nation, to make the remainder of the return trip to England overland through these countries. He offered to pay him 15 pounds sterling for his story when he reached London. Davison decided to risk it. Shortly thereafter, Dr. Gardner arrived from Salonika where Dr. Hodges was making a good recovery from typhus. Because Gardner was also an American, he and Davison decided to make the overland return trip together.

With new passports from the American Consul, they made their way across northern Italy and into Austria. At the German border they were held and interrogated for three hours but were finally allowed to proceed with two soldiers accompanying them as guards. They shook their guards in Munich and thereafter had no further difficulties until later when they reached the Dutch border.

In the meantime they visited Heidelberg, Wiesbaden, Frankfurt, and Cologne, including some German military hospitals. They even learned from a talkative German officer convalescing at one of the pensions where they stayed that Germany was planning soon to use poison gas as a weapon.

Although they were arrested at the border when they tried to leave Germany, they were finally released after a few hours of interrogation. Fortunately before leaving Italy they had had the foresight to book reservations on a Dutch ship as if they were returning directly to the States out of Rotterdam. The Germans checked on these and decided they were not spies. When Davison and Gardner reached neutral Holland, they, of course, canceled their reservations to the States and crossed the channel to England.

Davison gave his interview and collected the 15£ from the *Daily Mail* editor.[13] Unfortunately the British authorities failed to heed or take seriously his story about the German's plans to use poison gas. Just ten days after his return to England, the Germans, for the first time, used chlorine gas against the unsuspecting and totally unprepared Allied forces at Ypres. This resulted in a serious German break-through in Flanders and a huge number of British, French, and Canadian casualties.

During the summer vacation in 1915, Penfield planned to study anatomy, in keeping with Osler's advice, but in Rome or Geneva, which would give him his first chance for some sight-seeing and traveling. Although discouraged by both the American consul and Cook's Travel Agency because of the war conditions on the continent, Penfield set out with two other American Rhodes scholars for Italy and Switzerland by way of Paris and southern France.

In Italy, which had just entered the war against Austria, Penfield and his companions were suspected of being spies and were followed everywhere and frequently searched and harassed by officials and border guards. Despite this they were able to visit a number of Italian cities but were turned back when they tried to visit Venice.[14] When they reached Switzerland, Penfield found the medical schools in Geneva and Lausanne closed for the summer so he spent the remainder of the vacation period taking a course in anatomy at Edinburgh, Scotland.

For his 1915 summer vacation, Holman, went to France to work at the French Red Cross hospital at Ris Orangis, south of Paris. Then, finally tiring of the lull periods in this rear-echelon base hospital, Holman volunteered to work at the front where he spent the remainder of his vacation as a private in the French Army working as an infirmier, or male nurse, and ambulance

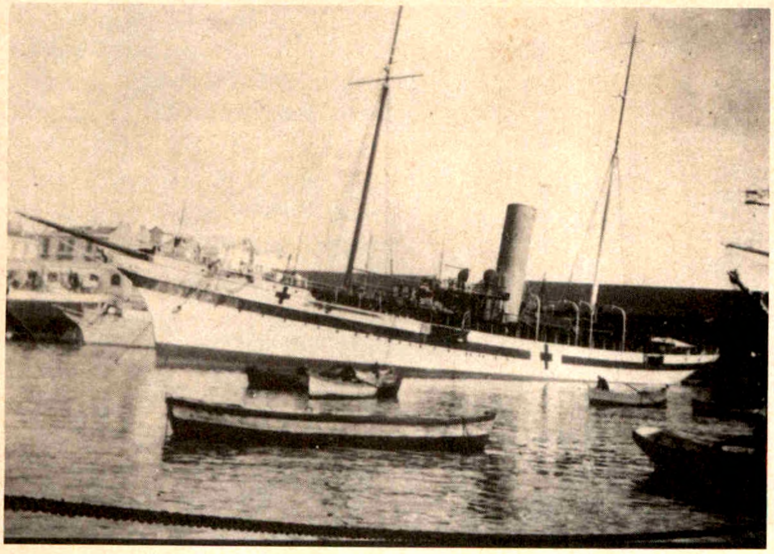

FIG. 5. Sir Thomas Lipton's yacht, *The Erin*, in the harbor at Salonika, Greece. Just a day or two before *The Erin* sailed for Italy with Davison as a Lipton passenger guest, the British had declined Lipton's offer of *The Erin* as a hospital ship for the Dardanelles campaign. *The Erin* was sunk by a German submarine in the Mediterranean in April 1916. A short time later in a reply to Davison,[12] Lipton wrote: ". . . I am consoled to some extent by the recollections of many happy days spent aboard in company with delightful friends, including your good self . . . she went down doing her bit . . . as recently as the 19th April, she herself sunk an enemy submarine by gunfire off Syracuse, Sicily". (Photo courtesy of Davison Archives Duke University Medical Center.)

driver at a French field hospital just behind the lines at Pagny-sur-Meuse.

Penfield finally got his chance to do some war work in France during his vacation at the end of the fall term in 1915. Like Holman, he was taken on at the French Red Cross hospital at Ris Orangis. Because of the personnel shortage, he was soon given intern-level responsibilities with a ward to look after (Fig. 6). For a beginning second year medical student to be doing the work of a real doctor was a great thrill, and he looked forward with enthusiasm to returning to the same hospital during his next vacation in the spring.

As soon as the winter term was over in March 1916, Penfield went to Folkestone, the only channel crossing port still open to civilians, and boarded the channel steamer "Sussex" to return to France. There were a number of Americans on board, including Professor J. Mark Baldwin, a prominent Baltimorian and friend of President Wilson, along with his wife and attractive daughter. The Baldwins had visited Sir William and Lady Osler just the day before.

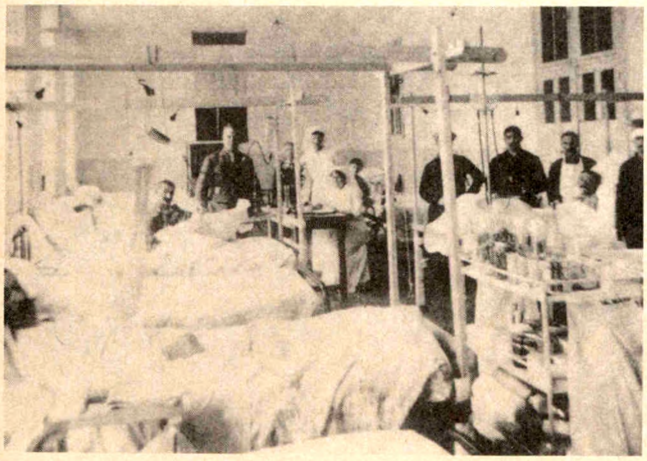

FIG. 6. Penfield's surgical ward at the Red Cross Ambulance Hospital, Ris Orangis, France, Winter 1915. (Courtesy Dr. William Feindel, curator Penfield Archive, Osler Library, McGill University.)

Late that afternoon after embarking, Penfield stood talking with Miss Baldwin on the main deck on the bow of the ship. A short time before they had passed some flotsam and floating bales of cotton, apparently from a recently sunken ship. Suddenly, without warning, there was a deafening explosion. Penfield, though dazed, remained conscious while turning slowly in the air along with much debris high above the bow where he had been blown by the explosion. For a moment, he feared he was going to fall into the sea.[2,15–18] Instead, he crashed down amidst the debris on the deck and suffered a severely injured leg.

The ship had been struck by a torpedo in the bow almost directly beneath where he and Miss Baldwin had been standing. It was evident that the remaining portion of the bow was about to break off, and although only able to crawl, he helped pull aft those still on the bow before it broke loose and sank. He made a futile search for Miss Baldwin. Penfield learned later she had been saved but had been severely injured. He fashioned a make-shift splint for his leg and with aid from others, did what he could to help the wounded.

The life boats were lowered and people began abandoning ship and even jumping overboard. The ship, however, continued to float without its bow (Fig. 7), and gradually as night came on, the badly leaking life boats and rafts that had not floundered returned to the ship (Fig. 8). The explosion knocked out the ship's wireless. Hours later,

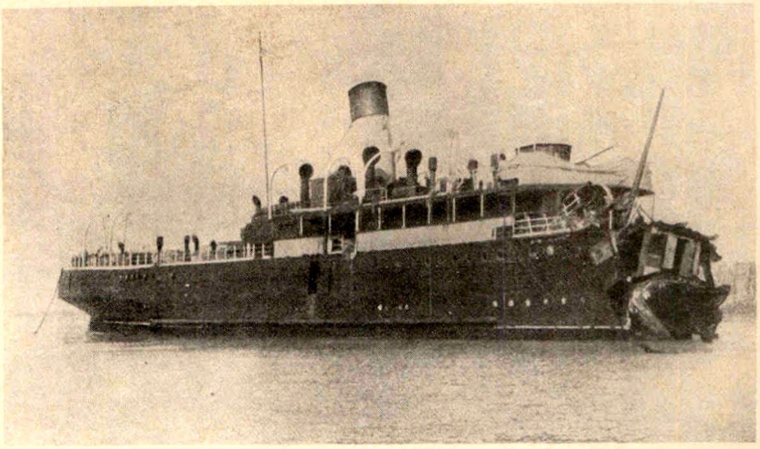

FIG. 7. The *Sussex* still afloat but minus her bow, which broke off and sank a short time after being struck by the torpedo. (From L'Illustation, Paris.[18])

when it was finally repaired, the operator reported an incorrect position, which delayed the arrival of the rescue vessels. It was nearly midnight before they were located by a French trawler and a British destroyer. Penfield was taken to a naval hospital at Dover, where he was found to have a fractured and badly contused leg.†

The torpedoing of the Sussex with so many Americans on board and with a fairly heavy loss of life made international headline news.‡ Penfield's rescue work and his efforts in treating the wounded while injured himself received much laudatory comment in the press. When he returned to Oxford, the Oslers insisted that he convalesce in their home, where he stayed for about three weeks.

In his last year at Oxford, Davison became interested in orthopedics and for a time thought he might enter that specialty after he graduated. This interest led him and Penfield to the following experience in London as described in *Davison of Duke; His Reminiscences.*[10]

> Osler had suggested that Wilder Penfield and I should attend Sir Arbuthnot Lane's clinic at Guy's Hospital and gave us a letter of introduction to him. We arrived after Sir Arbuthnot had started operating so we donned white gowns and masks and were given seats in the operating room. Lane was applying his steel plates to a patient's broken leg and making very crude remarks about Americans in general and Fred H. Albee§ in particular. We gathered from Lane's complaints that Albee had spoken at the Royal Society of Medicine the preceding evening about his autogenous bone grafts and had said they were superior to Lane's steel plates, which acted as foreign bodies and would bend.
>
> After he had finished operating, he pointed to me and said, 'You look strong, just try and bend one of my plates.' Naturally, I had been annoyed by Lane's diatribe against my country so I did my best to bend his plate and succeeded. After all, I had been rowing for six years and had fairly strong hands and shoulders.
>
> Sir Arbuthnot's astonished face, as I handed him the bent plate, was purple. He called his assistant and bawled him out for not having the plate properly tempered. Lane selected a stronger plate and sarcastically said to me 'Try and bend this one.' I did, so he asked me my name, apparently expecting it to be 'Sandow.' I handed him Osler's note of introduction, and Sir Arbuthnot's belligerent manner immediately changed. He spent the rest of the day with Penfield and me trying to atone for his rudeness, and took us all over Guy's Hospital and drove us to the American Embassy in his car.

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†Years later, in 1926, Penfield received a war indemnity for his leg injury from the German government. He used these funds in the purchase of a farm on Lake Memphrenagog, east of Montreal, which he and his family thoroughly enjoyed as a vacation retreat throughout his later life. It was here, in his study overlooking the lake, that he did much of his later writing.

‡At least one of the "color stories" written about the Sussex affair was not very factual. The day after the torpedoing, the following dispatch appeared in the *New York Times.*[19]

> London, Sunday, March 26 (1916)–An eager throng waited at the Victoria station yesterday for the trains coming from Dover with the survivors of the Sussex.
>
> One of the most anxious in the crowd was the aged father of Wilder Graves Penfield, a Rhodes Scholar from New York, who was on his way to Paris to join the American Ambulance Corp.
>
> The elder Penfield collapsed when he was informed that his son was in a Dover hospital with a broken leg. His condition became so serious that he had to be put under medical attendance at the station. He wished to go to Dover to be with his son, but his condition was such that the journey was impossible.

Ironically Penfield had no close relatives living in England at the time, and his father had died 3 years earlier in 1913.

§Dr. Fred H. Albee was a noted New York orthopedic surgeon, a pioneer in bone grafting, and author of a well-known textbook of orthopedic surgery.

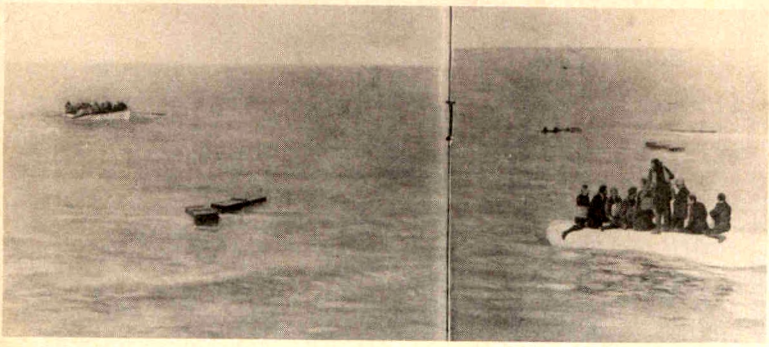

FIG. 8. Loaded *Sussex* lifeboat and life raft, which appear to be occupied mostly by men. As Penfield described it[15]: "I had already seen the first boat turn over and the people spilled . . . At first women were allowed to get in rather faster than men. But towards the end men began to jump for it and there were many women still on board." The lifeboats leaked badly and with the Sussex continuing to float in spite of her lost bow, those lifeboats and rafts which had not floundered had all returned to the ship by nightfall. (From L'Illustration, Paris.[18])

In August 1915 Davison began a research project under Professor Dreyer, Chief of Pathology, and Professors Ainley Walker and A. Duncan Gardner to determine the efficacy of a trivalent vaccine against typhoid, paratyphoid A, and paratyphoid B. He needed to study the immune response to the vaccine in rabbits. But because of a very strict antivivisection law dating back to 1876, to use animals it was first necessary to get a license from the British home office. This license was not only difficult and time consuming to obtain, but once granted the investigator was subject to annoying unannounced visits by the Home Office inspector.[20]||

After waiting a number of weeks for his license to arrive, and because no license was required for human beings, Davison finally used himself and his fellow medical students as volunteer experimental subjects. Later this work[23] would win him the Alvarenga prize.

That fall, Davison now in his third year of medical school, became a student intern at the Radcliffe Infirmary (Fig. 9). Holman replaced him in that position the next year. Both worked on Osler's service under Dr. F. H. Mosse, the resident medical physician.¶

Having been favorably recommended by both Osler and Sherrington, Davison and Penfield returned to the states in the fall of 1916 as transfers to Johns Hopkins University Medical School; Penfield as a third-year student, Davison as a fourth-year student. Holman stayed on at Oxford another year and transferred to Hopkins as a fourth-year student in 1917.

In later years Davison wrote Holman[24]# the following amusing anecdote relating to his Oxford experience that occurred near the end of his senior year at Hopkins:

> Leo Brady and other students told me it was only necessary to attend Professor Halsted's Thursday clinic because he called the students down from the benches, alphabetically and I did not need to go until the other students notified me. The day I attended, I was called down with six other seniors to examine a patient who had scandalized Dr. Halsted by acquiring an infection after a hernia operation. Dr. Halsted quizzed each of the students as to what they would do to treat this infected hernia. The other six students had no idea, and I brightly spoke up and said I would use the Carrel-Dakin method as I had worked with Carrel at the American Ambulance hospital at Neuilly, France and had just completed a paper[25] at Sir William's (Osler) urging on the Carrel-Dakin method before leaving Oxford.

||Holman, a third-generation American descendant of German immigrants, had been christened Emil Frederic Hollmann. After the outbreak of World War I, he became increasingly self-conscious of his obvious German name. He was sensitive to the frequent suspicion it provoked while working for the Belgium Relief Commission in Holland and occupied Belgium and also when he worked in France in the Red Cross Hospital and while a male nurse in the French army at the front. As he later wrote Davison:[21]

> I, too, applied for a license to experiment on animals and was favored by a visit from a representative of the British Home Office who interrogated me very brazenly, I thought, about my ancestors. You'll recall I spelled my name at that time Emil Hollmann.
>
> Finally, a little exasperate I said to him, 'look here! My ancestors came from the same place that the ancestor of your King did.'
>
> He got a little red and embarrassed and left almost immediately.

Apparently, this was the last straw for soon afterward Holman changed the spelling of his name from the unmistakable German Hollmann to Holman. Also he began omitting his middle name and when used, made sure it was spelled Frederic and not Frederick.

¶Fourteen years later (1930), while on a trip to China, Holman visited Dr. Mosse, who was then working at the medical school at Tsinan in Shantung province. Holman's humanism and kindness toward his fellow human beings was revealed in a letter he later wrote to Davison[21] about this China trip. Holman wrote: "I visited Mosse in Tsinan China in 1930 where he was doing a grand job in the Tsinan Medical school. I lived with him for two days and was struck by their apparent poverty. I remember forgetting my overcoat so that he could have a little more warmth in the rigorous winter of Tsinan."

#An almost-identical version appears in *Davison of Duke; His Reminiscences.*[10]

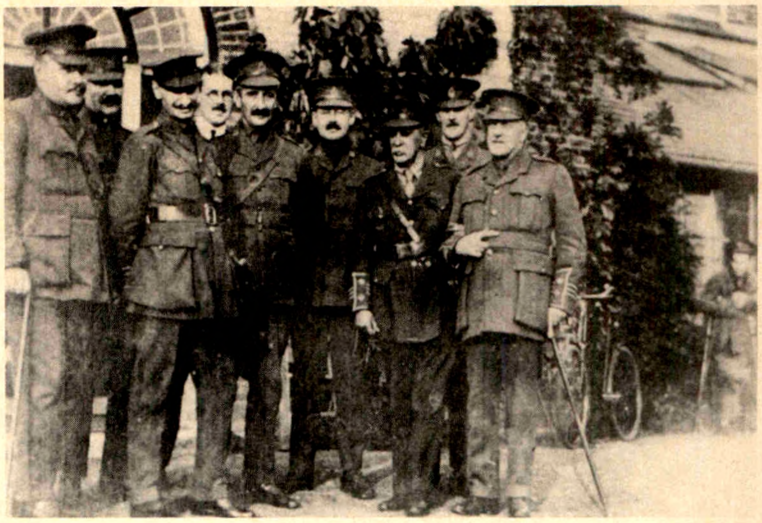

FIG. 9. Sir William Osler with the medical staff of the Canadian Military Hospital on Lady Astor's estate at Cliveden, England, in the spring of 1916. Osler, in his Canadian Army Colonel's uniform (he was an honorary consultant) is standing just to the right and holding the arm of his close friend Col. F. M. Mewburn (with the cane). Osler made rounds at this hospital each Monday morning and regularly took with him, Davison, then in his third year and student intern at the Radcliffe Infirmary, and occasionally Penfield, who was in his second year. Student Davison can be seen behind the others peering between the heads of the 3rd and 4th officers from the left. (Photo courtesy of Davison Archives Duke University Medical Center.)

> Halsted was amazed at my glib familiarity with a technique of which he had only heard rumors. I was as good as a huckster. At the end of the clinic Dr. Halsted asked for my name and offered me an internship in surgery. I thanked him graciously and said I was going overseas in six weeks.** He was charming and I often regretted my decision.

With so many extracurricular activities, including athletics, in which all three participated, (Fig. 1) one might wonder how they ever found time for their medical studies and student assignments.

Holman's application to Johns Hopkins when he transferred from Oxford for his senior year was once described by Alfred Blalock.[26] Dr. Blalock concluded that at Oxford, Holman had been one busy student. His application showed that by the end of his third year at Oxford, he had attended 39 autopsies and on 33 he had acted as prosector. He had anesthetized more than 100 patients and removed the tonsils and adenoids from 24. He had performed one herniorrhaphy and a number of amputations. During the obstetrics course, which all Oxford students took at the Rotunda hospital in Dublin, Ireland, he had participated in 67 deliveries, 31 of which he conducted personally.

Such were some of the days of these three Yankee medical students at Oxford from 1913 to 1917.

Wilburt Davison graduated from Johns Hopkins in 1917. After his Army service he returned to Hopkins for a pediatric residency, where he then joined the faculty and later became Assistant Dean. In 1926 he was chosen to organize and become the first Dean of the Duke University Medical School.

Wilder Penfield graduated from Johns Hopkins in 1918. after an internship at Peter Bent Brigham Hospital under Cushing, he returned to Oxford and London for 2 years of study in the neural sciences. After he became a neurosurgeon, he was attracted to McGill University, where a few years later he founded and became the first director of the Montreal Neurological Institute.

Emile F. Holman also graduated from Johns Hopkins in 1918. He stayed at Hopkins in surgical training and was Halsted's last resident. After further Surgical training at Harvard and Case Western Reserve, he was chosen Chairman of Surgery at Stanford University, where he had a long and distinguished career.

Acknowledgments

The author is extremely grateful to the literary executors of Wilder G. Penfield and to Dr. William Feindel, curator of the Penfield Archives,

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**In the first week of June 1917, after the close of the Hopkins school year, both Davison and Penfield married. Both embarked, almost immediately, for France and took their new brides with them. Davison sailed as a 1st lieutenant medical officer with the first contingent of the American Expeditionary Force. Penfield, now having completed his third year of medical school, returned with his bride to the same French Red Cross Ambulance Hospital but at its new location at Rue Piccini, Paris.

By the end of that summer, Penfield had about decided to join the American Army as an orderly in the medical corp and stay overseas while his wife continued working as a Red Cross volunteer. However he encountered a former, elder friend, Johns Hopkins surgeon, Dr. J. M. T. Finney, who was now a brigadier general and the chief surgical consultant to the American Army in France. Penfield had become acquainted with Dr. Finney while an undergraduate at Princeton and had worked one summer as tutor and companion to Dr. Finney's sons at the family vacation home in Chester, Nova Scotia.

During their Paris reunion, General Finney convinced Penfield that he should return promptly to Hopkins and complete his fourth year of medical school.

Soon thereafter, the Penfields sailed for the States aboard the S. S. *Rocambeau.* One of their fellow passengers was the British Minister of Munitions, Winston Churchill.

Osler Library, McGill University, for permission to use information derived from Dr. Penfield's papers of his early Oxford years, and to use Dr. Penfield's photograph for Figure 1.

The author wishes to thank Dr. Jay M. Arena of the Duke University Medical Center for permission to quote from *Davison of Duke; His Reminiscences.*[10]

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A Manometric Study of Anal Fissure Treated by Subcutaneous Lateral Internal Sphincterotomy

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A prospective, manometric trial of anal fissure treated by subcutaneous lateral internal sphincterotomy (SLIS) was designed to elucidate the pathophysiology of this condition. Anorectal manometry with a closed, precalibrated, water-filled microballoon using the station pull-through technique was performed on 13 patients with anal fissure before, and at one and 150 days after SLIS. The results were compared with 13 control subjects, matched for age and sex, who had no history of anal disease. Both resting pressure (RP) and maximum voluntary contraction pressure (MVCP) were measured at centimeter intervals of the anal canal. At all levels RP was significantly higher in the preoperative patients compared with controls ($p < 0.0001$). After operation RP fell significantly at all levels with the result that there was no significant difference in RP between postoperative patients and controls, except at 4 cm from the anal verge, where there remained a significant elevation in RP in the postoperative group. There was no significant difference in the two sets of postoperative manometric results. All patients underwent rapid healing and resolution of their symptoms. MVCP did not change significantly after operation, nor did it differ from the control values. This suggests that the increase in RP is due to activity of the internal anal sphincter. This over-activity is present throughout the entire length of the internal anal sphincter and sphincterotomy of its lowest portion returns RP to normal values throughout most of the anal canal.

ANAL FISSURE IS the most common cause of acute anal pain and in the most severe cases becomes almost incapacitating. However, despite this, its etiology and pathophysiology remain obscure. Previous studies in the literature[1–14] have been conflicting and this prospective, manometric study was designed, by comparing fissure patients with controls, to determine the relative activity of the internal and external sphincters and to examine the effect of subcutaneous lateral internal sphincterotomy (SLIS) on patients with anal fissure.

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Materials and Methods

Thirteen patients (nine women and four men) with a mean age of 45 years (range, 25 to 75 years) with a symptomatic anal fissure confirmed on physical examination, were entered in the study. SLIS was performed under general or spinal anesthesia in the lithotomy position. The operative technique involved infiltration with 1% xylocaine in the submucosal and intersphincteric planes followed by an annular stab incision in the left lateral perianal region. Scissor dissection was then performed in the above planes to the level of the dentate line. The internal anal sphincter was then divided to this point and the length of the sphincter division was recorded in centimeters.

Anorectal manometry was performed on the fissure patients before and then after operation on days 1 and 150. Thirteen control patients matched for age and sex with no history of anal disease were also studied manometrically. No anal manipulations were performed before manometry to avoid the effects of anal dilatation on sphincter pressures. Manometry was performed using a precalibrated, closed, water-filled, 2.5 mm microballoon (Fig. 1) connected *via* a 1.5-mm nondistensible polyethylene tube to a pressure transducer and the results were printed on a Hewlett Packard chart recorder. The patients were placed comfortably in the left lateral position. Measurement of resting position (RP) relative to atmospheric pressure was then performed using the station pull-through technique, with recordings in centimeters of water (H_2O) made from rectal ampulla to anal verge, at centimeter intervals. The procedure was then repeated, this time with maximum voluntary contraction, to determine the activity of the external anal sphincter. Maximun vol-

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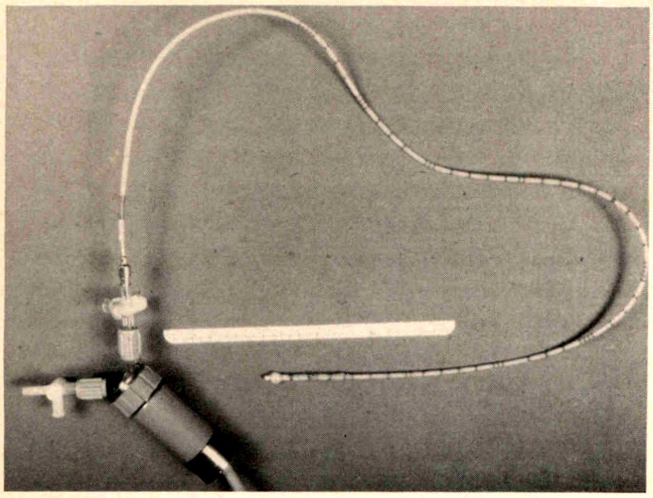

FIG. 1. Microballoon, catheter, and transducer used for anal manometry.

untary contraction pressure (MVCP) was defined as the increment of maximum pressure recorded above RP. Despite initial apprehension, none of the patients complained of discomfort with the procedure, despite close questioning.

All data was assessed by calculation of normal distribution plots and found to be normally distributed. The paired Student's t test was used to compare the pre- and postoperative results. The nonpaired Student's t test was used to compare the fissure patients to the controls. All calculations were performed on a DEC PBS/11/23 computer using a Minitab statistical package.

Results

RP was found to be significantly higher in the anal fissure patients compared with the control group at the 1-, 2-, 3-, and 4-cm levels from the anal verge ($p < 0.0001$; Fig. 2). Examination of the results in the series of two postoperative manometric sessions revealed no significant difference, so the results of day 1 were used to simplify the comparison (Fig. 3).

After subcutaneous, lateral internal sphincterotomy, there was a significant fall in RP at all four levels of the anal canal compared to the preoperative values ($p < 0.0001$), despite the fact that the mean recorded length of the sphincterotomy was only 2 cm.

As a result of this fall in RP, the values at the 1-, 2-, and 3-cm levels were statistically similar to the control values. However at 4 cm from the anal verge, despite a significant fall ($p < 0.0001$), the RP remained significantly higher than the control level ($p < 0.0015$; Fig. 2).

Examination of the MVCP, which is largely a reflection of external sphincter activity, revealed no significant change after operation (Fig. 4). All patients had good to dramatic relief of their symptoms and usually had almost painless bowel motions within two days. One patient had mild impairment of flatus control for about ten days. Aside from this the only morbidity associated with SLIS was some slight bruising at the operative site.

Discussion

Treatment of anal fissure by sphincterotomy is not new and was first suggested in 1818 by Boyer. The SLIS used in this series was basically a modification of Parks'[15] and Notaras'[16,17] techniques.

Eisenhammer[18,19] proposed that in patients with anal fissure, spasm of the internal anal sphincter occurred, resulting in a chronic contracture and thus producing a chronic fissure. Duthie and Bennett,[1] using a water perfusion technique, found no difference in manometric pressures between fissure patients and controls. Keighley[2] also found no manometric difference in seven patients with chronic anal fissures compared with 20 controls. However, in a later and larger study with Arabi,[3] he found that there was increased RP in patients with anal fissure.

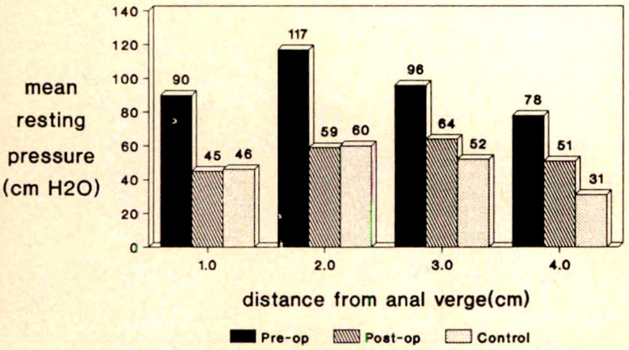

FIG. 2. Resting pressure.

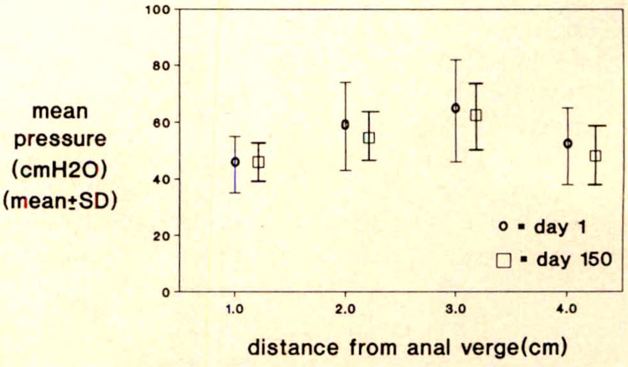

FIG. 3. Postoperative resting pressure (day 1 *versus* day 150).

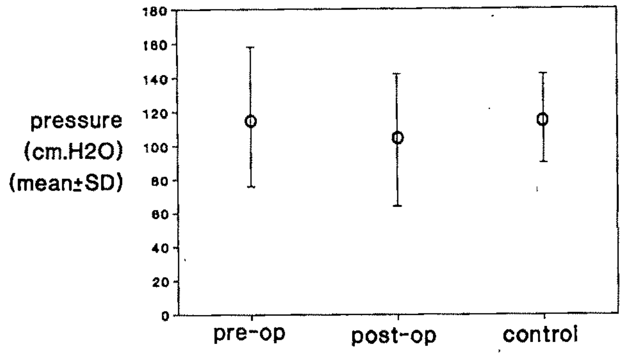

FIG. 4. Maximum voluntary contraction:

Using latex balloons Abcarian[8] could find no statistical difference in RP in eight patients with chronic anal fissure compared to ten controls.

In our study we found a statistically significant higher pressure in patients with anal fissure compared with a controlled group. This result correlates with most other published series.[3,4,6,7,9,11–14] However Arabie[3] and Kuypers[9] did not include postoperative results in their series. In contrast to Olsen[14] and Abcarian,[8] who found no significant reduction in RP after lateral internal sphincterotomy, we found up to a 50% reduction in RP after this procedure, and this is in agreement with a number of other series.[4,5,7,10–12] In the studies by Marby[5] and Boulos,[10] comparative statements are difficult because no control groups were included. Nothman[6] described an abnormal rectoanal inhibitory reflex that was characterized by an overshoot contraction following a normal relaxation. However, even though he found elevated RPs before operation, he did not mention postoperative values aside from describing loss of this overshoot phenomenon. Kuypers[9] believed that because the internal anal sphincter reacted normally, there was no spasm of the internal anal sphincter, and was unsure whether the increase in RP was due to activity of the internal or external sphincters.

Most authors, who have found increased RP in patients with anal fissure, have not been sure if the high pressure found is a cause or result of the anal fissure. Gibbons[13] believed anal hypertonia produced ischemia that prevented the fissure from healing; however his series included no operative results for comparison. Most authors have reported one value for RP in contrast to our series, which gives values at four levels of the anal canal. Cerdan[7] also reported his results in this manner. We found significant reductions in RP at all levels of the anal canal, but the postoperative values at 1, 2, and 3 cm from anal verge after SLIS were still in the normal range, despite the fact that the internal anal sphincter had been divided over its lower half. If this procedure had been done on normal patients, a decrease in RP would be expected, as can occur in inadvertent internal sphincter division during hemorrhoidectomy. This would appear to suggest that there is an underlying hyperactivity of the internal anal sphincter. This is also supported by the finding that at the 4-cm level from the anal verge, despite a significant postoperative reduction and resolution of the fissure, the RP was still significantly higher than controls, which suggests some persistent spasm in the internal anal sphincter ($p < 0.0015$). These results are similar to those found by Cerdan;[7] however he did not comment on the persistence of the postoperative RP above that of the control subjects in the upper anal canal, as recorded in his paper. Nor did his study include measurement of MVCP, which needs to be recorded, to be more certain that the RP found is due mainly to activity of the internal anal sphincter. This is also the only series that reports the sphincterotomy length (2 cm), and yet the total length of the internal anal sphincter is affected by the procedure. Only two other series, by Hiltunen[11] and Chowcat,[12] have used controls matched for age and sex, as in this series. This is an important feature because manometric pressures have been reported to change with age.[20]

The MVCP did not change after operation and remained similar to the control levels. This is in agreement with other series and suggests that the higher RP found in patients with an anal fissure is due to increased activity in the internal anal sphincter. These results further suggest that there is probably an underlying abnormality of the internal anal sphincter, which may predispose these patients to anal fissure.

RP is significantly elevated in patients with anal fissure and it results from overactivity of the internal anal sphincter over its entire length. SLIS of the distal half of the internal anal sphincter returns RP to normal values throughout most of the anal canal, and it would appear that there is indeed a basic abnormality in the internal anal sphincter, which consists of overactivity, and this may predispose these patients to the development of anal fissure.

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Bile Reflux in Postoperative Alkaline Reflux Gastritis

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This study evaluates enterogastric reflux (EGR) levels in patients with and without symptoms of postoperative alkaline reflux gastritis (PARG) after gastric surgery. The bile acids (BA) present in the gastric juice were quantified by thin-layer chromatography and spectrofluorometry. The mean BA concentration for controls was 2.25 μmol reflux/hour, for 15 asymptomatic patients 47.94 and for 15 patients with symptoms of PARG 125.79. After biliary diversion by a Roux-en-Y anastomosis in the latter, their BA concentrations markedly decreased. Symptoms of PARG disappeared in 13 of these patients after surgery, and relapsed in only one during a 4-year follow-up. The remaining two patients had the lowest preoperative BA levels in this group. These results indicate that EGR is increased after gastric surgery more markedly in patients with symptoms of PARG, and that patients who have high levels of EGR (more than 80 μmol BA reflux/hour) clearly benefit from biliary diversion.

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POSTOPERATIVE ALKALINE REFLUX gastritis (PARG), first recognized by Van Heerden et al.,[1] is a clinical syndrome diagnosed with increasing frequency in patients who have been subjected to surgical suppression of the pyloric sphincter function or to gastrojejunal bypass. Although histologic lesions involving the gastric mucosa can be found in all patients after gastric surgery, only a small proportion of them develop symptoms attributed to PARG. Several studies have shown that gastritis is mainly caused by the enterogastric reflux (EGR),[2-4] but the intrinsic physiopathologic mechanisms through which the existence of EGR determines the appearance of clinical symptoms are not clearly established. While medical treatment of PARG is usually ineffective,[5,6] the Roux-en-Y biliary diversion has shown satisfactory results,[7-9] although not in all cases.[10-12] Attempts have been made to predict the success of this surgical procedure by determining the preoperative levels of EGR, but this issue is still controversial.

The aims of the present study were the quantitation of the EGR, by the analysis of its bile acid (BA) content, in patients with symptoms of PARG and the comparison of their results with those of asymptomatic patients after gastric surgery and of healthy subjects. We also studied the results of a biliary diversion by a Roux-en-Y anastomosis during a 4-year follow-up period.

Material and Methods

Subjects

Three groups of 15 subjects each were studied (Table 1). Informed consent was obtained from all subjects before the study. Group I included subjects in good health, in whom any gastrointestinal disease was ruled out by clinical history and examination. Patients of group II had previous surgery (Table 2) for benign gastric or duodenal ulcers. None of these patients had any symptoms of digestive or other concomitant diseases.

Patients of group III also had had surgery for ulcer disease but referred symptoms suggestive of PARG. All had epigastric pain, 14 had bilious vomiting, 9 experienced weight loss, and 2 were anemic. The time interval between surgery and the onset of symptoms ranged from 10 months to 23 years. The existence of other diseases, such as hiatal hernia, recurrent ulcer, gastric bezoar, biliary lithiasis, and chronic pancreatitis, was ruled out by history and several examinations, including barium meal, echography, and gastroscopy with biopsy. All these patients were subjected to a biliary diversion by a Roux-en-Y

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TABLE 1. *Characteristics of the Three Groups of Subjects Studied*

Group	Sex (m/f)	Age (years)	Time After Surgery (years)
I	8/7	42 ± 14	
II	12/3	47 ± 10	6.9 ± 1.5
III	12/3	48 ± 10	8.2 ± 7.1

anastomosis 60 cm from the gastric remnant; in three patients who did not have previous truncal vagotomy, this was simultaneously performed.

Methods

After an overnight fast a nasogastric tube (#18) was introduced under radiologic control and fixed in place 7 cm from the gastrointestinal junction. The gastric content was collected by continuous suction during 24 hours and stored at −20 C until analysis. Samples were obtained under the same conditions from all subjects. Patients of group III were studied again 15 days after the Roux-en-Y diversion.

The BA present in the gastric juice was extracted by adding 1 mL of the sample to 10 mL of a mixture of ethanol/ether (3/1 v/v), shaking vigorously for ten minutes, and centrifuging at 1500*g* for 15 minutes. The overlying solution was evaporated under a nitrogen stream and the residuum dissolved in 1 mL of ethanol.

For the analysis of the conjugated BA, amounts of 5 μL to 10 μL of the extracts were applied on silica gel chromatoplates (Merck, Darmstadt, GFR) and developed with a solvent mixture of 1-propanol/tetrachloroethylene/formic acid (13:5:2 v/v).[13] For the analysis of the free BA, 40 μL to 50 μL of the extracts were applied and developed with a mixture of isooctane/ethylacetate/n-buthanol/acetic acid (20:10:3:3 v/v).[14] The isolated BAs were detected as fluorescent compounds by thermal treatment of the plates in the presence of zirconyl chloride.[15] Quantitation was done by *in situ* spectrofluorometry with UV light at 366 nm (spectrofluorometer PM2K Zeiss), and automatic integration of the peak areas of each BA. The absolute amount of BA present in each band was then calculated on the regression line obtained from standard pure BA (Sigma Chemical Co, St. Louis, MO) developed on the same plate. Results were expressed as concentration of BA in μmol reflux/hour. Statistical comparisons were made with the Student's t test for paired and unpaired samples.

Results

Values for each BA and for the total BAs present in the gastric juice samples of the three groups are shown in Table 3. The mean values of total BAs and of each conjugated BA were significantly increased in groups II and III, with respect to those of group I. The same was true for group III results compared to group II. Free BA values were significantly increased only for the cholic acid in group II and the cholic and deoxycholic acids in group III, with respect to group I, and for the deoxycholic acid in group III, with respect to group II.

Conjugated BAs were detected in only eight of the healthy subjects (group I), and free BAs were found in none of them. Of the eight subjects with detected BA, four were men and four were women; there were no significant differences between both sexes. The mean age of the eight subjects with BA detected was 51 ± 12 years, while the age of the remaining seven subjects was 32 ± 7 years ($p < 0.005$). There were quantitated amounts of conjugated BA in all patients of group II, and free BA in nine patients. Similarly there were conjugated BAs present in all patients of group III, and free BAs in 11. Considering the individual values of total BA, it was found that 4 of the 15 patients of group III had a concentration lower than 80 μmol reflux/hour, while none of group II had values higher than this level (Fig. 1).

After a biliary diversion by a Roux-en-Y anastomosis, there was a marked decrease in the gastric juice BA of all patients of group III (mean, 1.20 ± 0.58; Fig. 2). Conjugated BAs were detected in only four patients, with values ranging from 2.7 μmol to 8.2 μmol reflux/hour. Free BAs were not found in any case. This reduction in the BA concentration was accompanied by a marked improvement of the symptoms in most patients. Clinical evaluation showed that ten patients were completely asymptomatic after biliary diversion. Three other patients reported important improvement of the symptoms but had slowing of the gastric emptying; in these cases a vagotomy was performed at the same time as the biliary diversion. Slowing of gastric emptying was assessed radiographically by an increase in retention time of a barium meal in the stomach cavity. The remaining two patients continued with gastric pain but no bilious vomiting. These two patients had the lowest preoperative BA levels in the group (36.1 μmol and 31.2 μmol reflux/hour, respectively).

During the 4-year follow-up after biliary diversion, of the 10 patients with completely satisfactory results, 8 were asymptomatic, 1 underwent surgery for gastrointestinal

TABLE 2. *Operations Performed in Patients of Groups II and III Before Entry into the Study*

Operation	Group II	Group III
Pyloroplasty + truncal vagotomy	9	9
Billroth I + truncal vagotomy	2	—
Billroth II gastrectomy	—	3
Billroth II + truncal vagotomy	4	2
Gastroenteroanastomosis + truncal vagotomy	—	1

Group II, asymptomatic patients; group III, patients with symptoms of PARG.

TABLE 3. *Concentration of the Different Bile Acids Present in the Gastric Juice of the Three Groups of Subjects Studied.*

Bile Acid	Group I	Group II	Group III
Taurocholic	0.62 ± 0.22	11.00 ± 1.79*	19.03 ± 3.05*†
Taurodeoxycholic + taurochenodeoxycholic	0.06 ± 0.06	5.85 ± 1.43*	16.75 ± 3.62*†
Glycocholic	0.40 ± 0.25	14.55 ± 2.46*	33.29 ± 8.18*†
Glycodeoxycholic + glycochenodeoxycholic	1.16 ± 0.43	16.01 ± 3.64*	53.25 ± 9.05*†
Cholic	—	0.29 ± 0.10*	1.71 ± 0.82
Deoxycholic	—	0.02 ± 0.02	0.37 ± 0.13*†
Chenodeoxycholic	—	0.13 ± 0.06	1.24 ± 0.74
Lithocholic	—	0.05 ± 0.02	0.13 ± 0.04
Total BA	2.25 ± 0.60	47.94 ± 5.32*	125.79 ± 20.89*†

Values are mean ± SEM, expressed in μmol reflux/hour.
* $p < 0.01$ when compared to group I.
† $p < 0.05$ when compared to group II.

Group I, control subjects; group II, asymptomatic patients; group III, patients with PARG.

bezoar, and 1 had relapsing gastric pain. The three patients with slowing of the gastric emptying only complained of postprandial bloating. The last two patients who did not improve after surgery continued with similar symptoms.

Discussion

The results of this study show that EGR, quantitated by the analysis of the BAs present in the gastric juice, may be present in normal subjects, but they are largely increased in patients who have had surgery for peptic or duodenal ulcers. EGR was higher in patients with clinically evident PARG than in those without symptoms. Moreover after a biliary diversion the BA content of the gastric juice was markedly decreased and the EGR reduction was related with improvement of the symptoms in most cases.

Wormsley[16] and others[17,18] suggested that EGR occurs to some extent in man physiologically, in fasting, and also after meals. Our results support this conclusion; we found quantifiable amounts of BA in the gastric juice of 8 of the 15 healthy subjects studied. The fluorescence detection

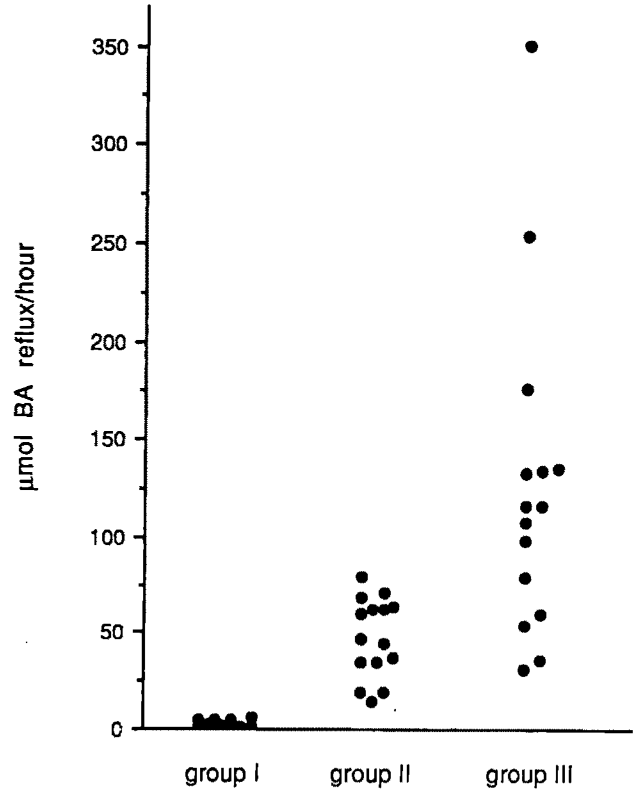

FIG. 1. Total BA values in the gastric juice of control subjects (group I), asymptomatic patients (group II), and patients with PARG (group III) after gastric surgery.

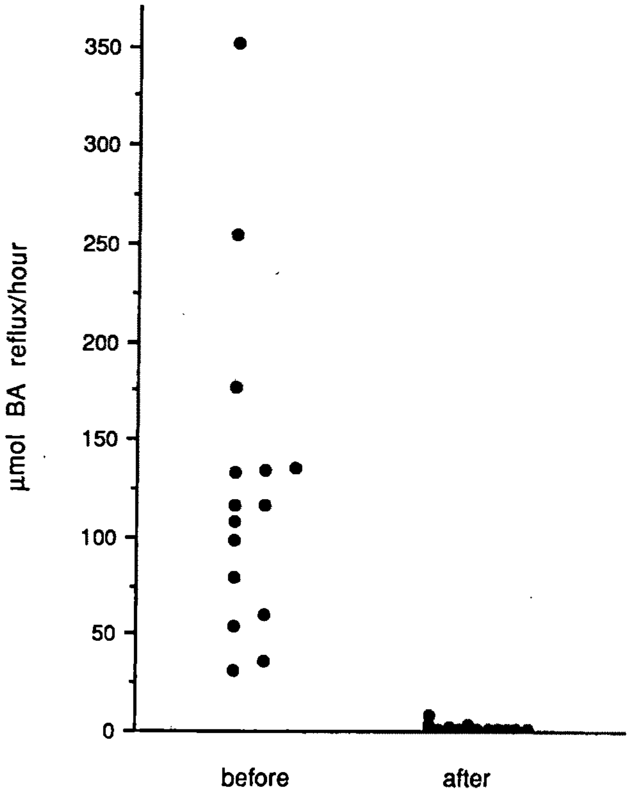

FIG. 2. Total BA values in the gastric juice of patients with PARG (group III) before and after biliary diversion by a Roux-en-Y anastomosis.

method used is highly sensitive, with limits of detection in the range of few nanograms of steroid compounds.[15] There were no differences between sexes. On the other hand, age seems to play a positive effect on the amount of EGR. It has been shown that the frequency of chronic gastritis and intestinal metaplasia also increases with age.[19] Therefore it may be suggested that EGR levels are progressively larger with increasing age, contributing to the appearance of gastritis. Alternatively the EGR might be similar in all healthy subjects, but the efficiency of the stomach content emptying during the third phase of the motor gastric cycle decreases with age. This would determine a longer presence of the intestinal content refluxed into the stomach. Other factors once suggested to promote EGR, such as smoking, alcohol, and caffeine, have not been considered in this study because the works by Yeomans et al.[20] and Niemela[21] clearly showed that they do not have any significant effect.

After gastric surgery removes the pyloric sphincter function, the amount of EGR largely increases. Some operated patients show clinical signs and symptoms consistent with a PARG syndrome.[1] Clinical history, radiologic examinations, gastroscopy, and biopsy must be performed to rule out other diseases of the digestive system that may be responsible for similar symptomatology. Several authors found good correlation between the degree of EGR quantified by different methods and the existence of symptoms of PARG.[2-4] We have used the quantitative analysis of the different BAs present in the gastric juice as an index of EGR. All patients of groups II and III had BA present in their gastric juice in much higher concentrations than the normal limit found in the control group I. The symptomatic patients had an average value of total BA almost three times higher than the asymptomatic group. All patients with total BA values greater than 80 μmol reflux/hour were overtly symptomatic, while there were patients of both groups between 30 μmol and 80 μmol reflux/hour (Fig. 2). The reasons that patients with similar levels of EGR may or may not have a clinical manifestation of PARG are unknown. One likely explanation is the variation in the defensive mechanisms of the gastric mucosal barrier, which would determine a different sensitivity of the mucosa to the EGR.[22] This would also explain the variability in the amount of time without symptoms after gastric surgery in patients with similar amounts of EGR.

The presence of free BAs in the gastric juice of some patients is worthy of comment because these compounds are known to be more noxious than the conjugated BAs for the gastric mucosa. BAs are conjugated before excretion in the bile, where they are found as free compounds only in very small quantities.[23] The hypochlorhydria secondary to gastric resection allows the development of a more abundant microbial flora in the stomach.[24] Some of these micro-organisms can deconjugate BA by hydrolyzing peptidic bounds, as they do normally in the bowel.[25] Free BAs were present in a higher concentration and in more patients in group III than in group II, although the differences were not highly significant due to the low absolute values and their variability. Similar results have been shown by Gadacz and Zuidema,[26] but are argued by others.[27,28] From these results it can not yet be definitely concluded if the free BAs are especially responsible for the PARG.

We initially used medical treatment in our patients (metochlopramide, alkaline, or sedative drugs) with poor results. Cholestyramine was not used because it was shown to be ineffective in other studies.[5] Finally we decided to perform a biliary diversion by a Roux-en-Y anastomosis. The procedure proposed by Warshaw[29] was used in the first nine patients of group III in an attempt to predict those patients who could obtain benefit from the biliary diversion. Four patients had pain starting with the introduction of alkaline solution, one with acid solution, and four had no response. From these irregular results and the discordance with the clinical symptoms, we discontinued using this procedure. Moreover it is only an indication of the stomach tolerance to changes in pH, and not to the different compounds that constitute the reflux.

The biliary diversion was performed in all symptomatic patients, independent of the values found in the BA analyses. All cases had an uneventful postoperative course, although in three patients emptying of the gastric content was persistently slowed. In these three patients vagotomy had been performed simultaneously with the Roux-en-Y, while the remaining vagotomy had been done before. This suggests that the combination of both procedures slows gastric emptying. The postoperative analyses showed a marked reduction in the BA content of the gastric juice in all cases. Most patients experienced an important improvement of their symptoms. These results correspond to those obtained in other studies.[9,30,31] After a 4-year follow-up the results were completely satisfactory (Visick I), without symptoms attributable to gastritis in nine patients, and partially satisfactory (Visick II) in four (one case with mild relapse of PARG symptoms and three with slowing of gastric emptying). The two patients without improvement had the lowest preoperative BA values; this indicates that patients with a low level of EGR (below 50 μmols BA reflux/hour) do not benefit from biliary diversion surgery. Our long-term results showed a slightly better outcome than was found in previous studies.[27,32]

These results support the belief that EGR is the main causal factor in the development of PARG. However it is still unknown which components of the reflux are most responsible for damaging the gastric mucosa. The role of BAs remains controversial,[26,28] although they can be used as a reliable index of the existence and amount of EGR.

The predictive value of the BA levels found in gastric juice is difficult to ascertain. All our patients with values greater than 80 μmol reflux/hour were symptomatic and improved after biliary diversion. Patients within the range of 50 μmol to 80 μmol were symptomatic or not, but they can be considered, as a group, at high risk to develop PARG. Longer follow-up will help to establish if those patients of group II with high BA values will eventually have symptoms.

All surgical techniques that remove the function of the pyloric sphincter promote EGR, and experimental findings have shown that chronic exposure to bile or pancreatic juices has a damaging effect on the gastric mucosa.[33,34] These results suggest that surgical treatment of ulcer disease be performed only when medical treatment is clearly unsuccessful and of substituting the usual surgical techniques with more physiologic ones that would not induce an increase in ERG.[35]

Acknowledgment

The authors thank Dr. Antoni Sitges-Serra for his critical review of the manuscript.

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Book Reviews

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Surgery of the Liver. William V. McDermott, Jr. 560 pp. Boston: Blackwell Scientific Publications, 1989. $125.00.

SURGERY OF THE LIVER, edited by William V. McDermott, Jr., in 560 pages encompasses 26 chapters distributed among six parts. The parts of the book, the contributions of 43 authors, include

Part I—Historical Aspects of Liver Surgery
Part II—Basic Science Considerations
Part III—Assessment and Diagnosis
Part IV—Surgical Disorders and Techniques
Part V—Hepatic Trauma, Tumors, and Resection
Part VI—Special Problems in Liver Surgery.

The production quality of the book is excellent. The high-quality paper is well bound and the print is of size and quality that makes reading easy. The illustrations, figures, and tables are clear, well reproduced, and enhance the quality of the volume. The book's organization is excellent. The various well-chosen topics flow in a logical order that makes perusal and reading of the book easy. Each chapter is well referenced and the information in the chapters is uniformly timely and current. The content of the chapters is excellent. The writers are all experts and the majority are preeminent leaders in their respective fields. In addition to providing authoritative content, the writing in each of the chapters is outstanding.

In addition to organizing the book, initiating its creation, and writing two chapters, the editor, Dr. McDermott, provided editorial commentary to the chapters. This feature further enhanced the quality of this book.

Surgery of the Liver provides an excellent source of information to aid in the diagnosis and treatment of diseases of the liver. It will make an authoritative source of information for students and a handy reference or review source for residents and surgeons who care for patients with diseases of the liver. I highly recommend this book for those who are undertaking the challenge of caring for patients with liver disease. Study of this book will make their work more interesting and more effective.

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Surgical Management of Soft Tissue Sarcoma. Man H. Shiu and Murray F. Brennan. 297 pp. Philadelphia: Lea & Febiger, 1989. $58.00.

THIS COMPREHENSIVE BOOK represents the experience of a group of clinicians at one of our nation's leading Cancer Centers. These professionals have dedicated themselves to the diagnosis and treatment of soft-tissue sarcomas. Because of their relatively infrequent occurrence, these tumors are often treated inappropriately—all the more reason to consult this authoritative source. The authors emphasize the multidisciplinary approach that is essential to achieve the best results with these tumors. To provide the most current information concerning the various aspects of the overall management of these neoplasms, the two primary authors have chosen experts in the various disciplines. Progressing in an orderly fashion from a discussion of concepts and principles to sarcomas in various locations and finally addressing multidisciplinary treatment, the contributors supply clinicians with detailed information to ensure the best treatment for their patients. With their vast experience at the Memorial Sloan-Kettering Cancer Center, these specialists give cogent reasons for their conclusions. The important roles of staging and diagnostic imaging techniques are discussed. Factors primarily responsible for prognosis are detailed in a scholarly manner. Although surgical resection is the treatment of choice for most of these tumors, proper emphasis is given to the role of radiation therapy and chemotherapy. The book is well-written and well-illustrated with adequate documentation to support the views expressed. It is invaluable as a major reference for residents and other clinicians interested in soft-tissue sarcomas.

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Care of the Wounded in Vietnam. Robert M. Hardaway. 244 pp. Manhattan, KS: Sunflower University Press, 1988. $15.00.

BRIGADIER GENERAL ROBERT M. HARDAWAY, MC, USA (RET), with contributions from his associates, provides a personal perspective of a variety of aspects involving care of the wounded by the United States military during the war in Vietnam. Dr. Hardaway emphasizes the period between 1965 and 1967. Although the number of American surgeons serving in Southeast Asia during the Vietnam War, both partially trained and fully trained, might approach 1000, Dr. Hardaway is one of few to make the effort to document the experience. With younger associates who had personal experience, he adds his perspective from more senior military and medical levels.

The contents are organized for rapid identification and review covering the medical facilities in 1965 and 1967, identifying the wounded patient with various profiles, and including research activities. Specific chapters relate to the forward management of casualties, helicopter transportation of casualties in Vietnam, and specific hospital treatment in Vietnam in both Army and Navy hospitals, with an added chapter for anesthesia for combat casualties. References to previous reports are included at the end of most chapters. Photographs complement the text.

While this book of 220 pages emphasizes the personal experience of the author, augmented by collaborators and previous publications, it should be of general interest to anyone who was in Vietnam, who is interested in military medicine and surgery, or who is interested in the management of injured patients.

NORMAN M. RICH, M.D., F.A.C.S.
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General Thoracic Surgery, 3rd Ed. Thomas W. Shields. 1251 pp. Philadelphia: Lea & Febiger, 1989. $150.00.

THE THIRD EDITION of *General Thoracic Surgery*, edited by Thomas W. Shields, attempts to present a comprehensive review of the diagnostic, operative, and postoperative management of noncardiac pediatric and adult thoracic disorders. The text retains the organization of the second edition of 6 years ago, with discussions of anatomy and physiology followed by sections on preoperative evaluation, descriptions of operative procedures, and a systematic discussion of diseases affecting each organ system within the thorax. The final three sections are devoted to thoracic oncology and immunotherapy. The new edition includes a larger page size and expanded text. There are new separate sections dealing with magnetic resonance imaging, free jejunal transfers for esophageal replacement, adult respiratory distress syndrome, chest wall reconstruction, paraesophageal hernias, chylothorax, and Barrett's esophagus. Particularly lucid sections are those on surgical anatomy of the lungs, mechanics of breathing, the use and positioning of double lumen endotracheal tubes, lung transplantation, and esophageal hiatal hernia.

Although many authors have contributed to this text, the influence of the editor appears to be evident in consistent themes throughout the book. These include minimal emphasis on historical background, clear expositions of the diagnostic and therapeutic algorhythms, balanced discussion of controversial areas, and useful cross-referencing to other chapters in the book. The references for each chapter are thorough and current. Although there are many very recent developments in general thoracic surgery that are included in the text, such as the new staging systems for esophageal and lung cancer, the reviewer wished there had been a discussion of thoracoscopy and pleuroperitoneal shunts for pleural effusions. In addition the chapter on thoracic outlet syndrome had no discussion of the importance of distinguishing upper and lower plexus symptoms and contained no description of the renewed interest in the supraclavicular approach to this perplexing disease state.

The editor has given us a text that is lucid, authoritative, comprehensive, uniform, and current. All physicians who practice in the general thoracic area will find a wealth of basic science information and clinical experience on which to draw. Residents will find the text book useful in its emphasis on pre- and postoperative care and its descriptions of surgical procedures. The expense and comprehensive nature of the text may limit its usefulness to medical students, however.

THOMAS M. DANIEL, M.D.
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Organ Transplantation and Replacement. G. James Cerilli. 732 pp. Philadelphia: J. B. Lippincott, 1988. $99.00.

THIS IS THE FIRST of two books that has appeared since cyclosporine enabled the extraordinary expansion of organ transplantation. The objectives of the book are (1) to summarize the pertinent science, (2) to provide a detailed account of renal transplantation, (3) to describe the status of all other organs that are transplanted, and (4) to provide an introduction to artificial organ replacement. Happily the book fulfills these objectives.

However, it suffers from the malady of all multiauthor books. The basic immunology section is uneven. Some chapters are aimed at the level of medical students, and some are a challenge even for the transplant specialist. There is considerable repetition and overlapping among the chapters, but it is not particularly distracting. It may even be beneficial.

The book is divided into six parts. The first, Past, Present, Future, is concise and stimulating. Part II, Immunology, covers ten chapters. Part III, Renal Transplantation, which forms the bulk of the book, covering 21 chapters, is the strength of the text. Part IV, Other Organ Transplantation, serves as an update and summary of the various other organ transplants. Unfortunately the lag time in publishing a book renders this information from a particularly fast- changing field somewhat less than current, therefore, a little less compelling. The last two sections cover Artificial Organ Replacement (Part 5) and Special Topics in Transplantation (ethics and legal; Part 6).

The book is timely because it records the significant impact that cyclosporine has made on the art and science of renal transplantation and the clinical application of extrarenal transplantation. The cyclosporine experience was necessarily limited at the time of publication.

This is a badly needed comprehensive text in organ transplantation. It will be a useful reference for the medical student and a basic resource for those interested in the field. It must be compared with a similar book published shortly afterward of quite similar length and subject matter. The most striking comparison is that nine chapters in both books are written by the same authors, and therefore are similar in outline, content, and illustration.

JAY C. FISH, M.D.
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Letters to the Editor

June 10, 1989

Dear Editor:

We have read with interest the paper of Ringe et al. entitled "The Role of Liver Transplantation in Hepatobiliary Malignancy" in the January 1989 issue of *Annals of Surgery*.

In this analysis in 52 patients with hepatocellular carcinomas, liver transplantation had been performed, but only in four of them was a fibrolamellar variant evident. In addition only seven cases of orthotopic liver transplantation in fibrolamellar hepatocarcinoma (FLHC) have been published so far.[1]

To supplement these reported cases we want to submit another case report. A 65-year-old man, subjectively free from complaints, with no further signs of extrahepatic primary tumor or metastases, underwent an orthotopic hepatic transplantation (University of Innsbruck, Department of Surgery) because of multiple hypoechogenic lesions. Before operation the alpha 1-fetoprotein level was 23.8 ng/mL ($n < 3$). Histologic diagnosis was a multicentric fibrolamellar liver carcinoma in which—for the first time to our knowledge—expression of glucagon and some other neuroendocrine tumor markers (PHE 5, chromogranin) was shown immunohistologically.[2] Twenty months after hepatectomy the patient is alive and well and sonographically and CT proved free from recurrences or metastases.

Even though transplantations have been performed in only 12 cases of FLHC, this therapeutic regimen appears to be particularly indicated for this type of tumor because of its benign appearance and high 5-year survival rates,[3] as could also be proved by our case.

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August 25, 1989

Dear Editor:

Since the first descriptions of the fibrolamellar variant of hepatocellular carcinoma (FLC) by Edmondson, Craig, and Berman, an increasing number of publications have focused on this distinct clinicopathologic malignancy.[1–4] Indeed most of these authors claim the obviously better prognosis of FLC as compared to the ordinary hepatocellular carcinoma after resection and more recently also transplantation. So far the two largest series of patients with FLC receiving liver transplants have been published by Koneru and O'Grady, comprising nine and seven cases, respectively. Seven of those patients were reported to be alive with prolonged observation periods.[5,6]

Our own experience with liver replacement for FLC has been updated to the end of last year and now include a total of six patients. Thus two more cases could be added to the series published in the January 1989 issue of *Annals of Surgery*. Altogether three patients died with residual or recurrent tumor after 1, 11, and 28 months, respectively. At present the other three patients are alive without signs of recurrence 10, 11, and 36 months after transplantation.

Langsteger et al. describe the expression of glucagon and other neuroendocrine tumor markers in their own patient. Similar observations were reported by Paradonas[7] who showed an increased serum unsaturated vitamin B 12 binding capacity, and Collier[8] who found high serum neurotensin concentrations in patients with FLC underlining the specific biologic behavior of this tumor.

Again this emphasizes the need for accurate staging of patients with hepatobiliary malignancy assigned for liver transplantation, including the precise histopathologic diagnosis as an attempt to select those recipients with the most favorable prognosis.

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BURKHARDT RINGE, M.D.
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August 10, 1989

Dear Editor:

I wish to mention a correction that needs to be made to the article on the role of octreotide in the management of enterocutaneous fistulas, published in the July 1989 issue of *Annals of Surgery*.[1] Nubiola et al. write, "The octapeptide SMS 201-995 (Sandostatin) is one of those analoques; it has a half-life of eight hours and less influence on insulin secretion than somatostatin." Nubiola et al. cite a paper by Bauer et al.[2] that apparently defined this eight-hour half-life. However, on review of the paper by Bauer et al., I find no data to support the conclusion that octreotide has an eight-hour half-life.

Octreotide is rapidly and completely absorbed from a subcutaneous injection site. Peak levels occur within 30 minutes of the injection. The apparent elimination half-life is approximately 1.5 hours.[3] Kutz et al.[4] also report octreotide pharmacokinetic data collected in eight healthy subjects. They report an elimination half-life that ranged between 88 ± 20 minutes and 102 ± 16 minutes for different subcutaneous doses.

To say that octreotide has an elimination half-life of eight hours is incorrect. The drug does, however, possess pharmacodynamic effects that may last 8 to 12 hours, making dosing two to three times a day possible.

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PAUL E. MICHAELS, PHARM D.
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September 11, 1989

Dear Editor:

Dr. Michaels is right in pointing out our mistake concerning the half-life of octreotide. We quoted Bauer's work[1] to indicate that the biologic effects of this peptide were of longer duration that those of native Somatostatin and that, consequently, octreotide can be administered by the subcutaneous route every eight hours. We thank Dr. Michaels for giving your readers the appropriate information concerning octreotide's half-life.

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ANTONIO SITGES-SERRA, M.D.
Barcelona, Spain

August 14, 1989

Dear Editor:

In a recent article Gottlieb et al.[1] reported a "mesenteric traction syndrome" that consisted of tachycardia, hypotension, and facial flushing. It has been attributed to liberation of prostacyclin from the mesenteric vascular bed due to mesenteric traction.

This paper completely confirmed our own findings published in 1986 when we called this reaction "eventration syndrome" because it can be observed during many kinds of abdominal operations shortly after the gut has been eventrated, manipulated, or operated on.[2]

Additionally we observed an acute decrease in arterial oxygen tension during this phase due to pulmonary vasodilation and increasing intrapulmonary right-to-left shunt. When monitoring hemoglobin saturation with a pulse oximeter a fall in SaO_2 is regularly seen, especially in patients with compromised pulmonary function.

When patients are operated on in a combination of thoracic epidural with general anesthesia, a significant fall in mean arterial pressure can occur when prostacyclin-mediated vasodilation cannot be overcome by reactive increase of heart rate and cardiac output due to high sympathetic blockade.[3,4]

For these reasons the mesenteric traction or eventration syndrome should be familiar to anesthesiologists and surgeons because the most impressive cardiovascular changes occur during this stage of abdominal operations.

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WULF SEELING, M.D.
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September 6, 1989

Dear Editor:

I would like to thank Dr. Seeling for bringing to our attention that the mesenteric traction syndrome was previously described and named either eventration or evisceration of the gut. We agree with his previous report[1] that mesenteric traction syndrome is accompanied by a specific release of prostacyclin, which is likely to be responsible for the clinical manifestations.

Dr. Seeling's observation[1] of the decrease in PaO_2 due to an increase in ventilation perfusion mismatch is very interesting. We did not experience any periods of clinical hypoxemia or decrease in oxygen saturation monitored by pulse oximetry, although we were not actively measuring the PaO_2 during the bowel manipulation. Dr. Seeling's speculation that the decrease in arterial oxygen tension is due to an increase in shunting might well be true; we observed a trend of a decrease in pulmonary vascular resistance (PVR) during bowel manipulation. The mean control PVR was 138 ± 22 and it dropped during the mesenteric traction to 108 ± 14 dynes/sec/cm^{-5}, but was not statistically significant.

We noted that Dr. Seeling described hypertension during gut eventration in his patients anesthetized with neurolept anesthesia.[2] The syndrome caused by bowel manipulation includes *tachycardia*, *cutaneous flushing*, and *hypotension* and not hypertension. My guess is that the neurolept anesthesia group of patients in Dr. Seeling's study were too lightly anesthetized and therefore presented with an increase in blood pressure. As described in our manuscript, pain, sympathetic tone increase, and/or vagal stimulation accompanying the opening of the abdominal cavity can cause many other hemodynamic changes (such as hypertension and bradycardia) that should not be mistaken with the mesenteric traction syndrome.

In both our and Dr. Seeling's series the incidence of cutaneous manifestation was found to be high and comparable (54% and 58%, respectively).[1,3] While Dr. Seeling failed to find a correlation between 6-KPGF1 blood level and cutaneous manifestation,[3] we showed a good correlation of skin flushing to SVR, C.O., and prostacyclin blood levels.[1] This difference in our findings can be explained by the different anesthesia technique used, method of skin observation, or the fact that Dr. Seeling's series included fewer patients (13 patients compared to 31 in our series).

I would like to thank Dr. Seeling for his comments and contributions to the understanding of this syndrome and to the Editorial Board of *Annals of Surgery* who made it possible to share this information with the medical community.

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